Monitoring Health Concerns Related to Marijuana in Colorado: 2014

Appendix

COLORADO
Department of Public
Health & Environment

Appendix

Table of Contents

Bylaws
Retail Marijuana Public Health Advisory Committee

ARTICLE I: Name
The name of this committee shall be the Marijuana Health Effects & Public Health Policy Advisory Committee, herein referred to as the "Advisory Committee", created pursuant to Senate Bill 13-283, CRS 25-1.5-111, operating within the Department of Public Health and Environment, Disease Control and Environmental Epidemiology Division, herein referred to as the "department."

ARTICLE II: Purpose
The Colorado Department of Public Health and Environment is responsible for appointing a panel of health care professionals with expertise in cannabinoid physiology to examine and monitor health information relevant to marijuana use. The panel shall establish criteria for studies to be reviewed, reviewing studies and other data and make recommendations for policies intended to protect consumers of marijuana or marijuana products and the general public. A report of these findings will need to be presented to the State Board of Health, Department of Revenue and General Assembly by January 31, 2015 and every two years thereafter.

ARTICLE III: Members
Section 1. The composition of the Advisory Committee shall be comprised of individuals in the field of public health, approved prior to meeting commencement by the Executive Director of the department. These individuals will represent various organizations, including employees of the department, and have well-respected expertise in fields of study that are associated with the possible health effects or conditions related to marijuana use. The committee shall also include at least one representative from CDPHE, whose responsibilities will include organizing and leading this committee.

    A. Members of the Advisory Committee shall be appointed by the Executive Director of the department.

    B. The Advisory Committee shall consist of no more than 15 extra-departmental members.

    Members of the Advisory Committee should include at least:
- I. One member representing the field of drug epidemiology.
- II. One member representing the field of surveillance epidemiology.
- III. One member representing the field of medical toxicology.
- IV. One member representing the field of pediatric medicine.
- V. One member representing the Rocky Mountain Poison and Drug Center.
- VI. One member representing the field of psychiatry and drug addiction.
- VII. One member representing the field of pharmacology.
- VIII. One member representing the field of pulmonary medicine.
- IX. One member representing the field of obstetrics and gynecological medicine.
- X. One member representing local public health.
- XI. One member representing the Colorado School of Public Health.

C. The Advisory Committee shall consist of no more than 2 voting members representing the department, not including administrative or assisting research staff members.

D. The Advisory Committee shall consist of 1 alternate member from the department that will become a voting member in the unavoidable absence of other members representing the department.

ARTICLE IV: Duties of the Advisory Committee
Section 1. The Advisory Committee shall:
a) Ensure compliance with Senate Bill 13-283, CRS 25-1.5-111.
b) Review the scientific literature currently available on health effects of marijuana use.
c) Judge and openly discuss the science using expert medical opinion.
d) Come to consensus on population health effects of marijuana use based on current science.
e) Come to consensus on translation of the science into public health messages.
f) Recommend public health related policies based on the current science and expert medical discussion, which will presented in final report.
g) Recommend public health surveillance activities to address any gaps in knowledge discovered.
h) Identify and prioritize gaps in science important to public health.

Section 2. All Advisory Committee members shall sign a letter on behalf of the committee verifying his/her representation in the committee's final recommendations, per the categories listed in section 1.
Section 3. Members appointed to the Advisory Committee by the Executive Director shall serve on the committee for a one-calendar year term. A member may be reappointed to the Advisory Committee by the Executive Director every two years. There shall be no limit to the number of consecutive times any member can serve. Appointment of members is at the sole discretion of the department and Executive Director.
Section 4. Regular attendance and participation is vital to the purpose of the Advisory Committee. Members accept the duty and obligation to attend meetings either in person of by teleconference and shall provide advance notice if they are unable to do so. Repeat, unexcused absences may be considered an abdication of the appointment and may be grounds for terminating a member's appointment at the recommendation of the Advisory Committee. To terminate the member's appointment, at least one member of the Advisory Committee shall submit his/her recommendation to the other members of the Advisory Committee, which shall approve or disapprove the recommendation by majority vote.
Section 5. Members of the Advisory Committee shall serve without compensation.
Section 6. Any member of the Advisory Committee may resign from the Advisory Committee at any time by notifying the Committee Chair or his/her designee, in writing. If a member finds it necessary to resign from the Advisory Committee, he/she is encouraged to assist the department in nominating a suitable replacement and is encouraged to remain until a suitable replacement has accepted his/her nomination.
Section 7. Any member of the Advisory Committee may be recommended for termination by majority vote of the Advisory Committee or at the discretion of the Committee Chair, as a result of:
a) Resignation
b) Violation of the Advisory Committee Bylaws;
c) Failure to disclose conflict of interest;

d) Ineligibility of membership, including no longer representing the category to which a member was appointed under;
e) Material misrepresentation or fraud in any statement to the Advisory Committee or to the public;
f) Conviction of a felony;
g) Conviction of a misdemeanor, which is directly related to public health or education. This includes, but is not limited to, rape, sexual abuse, actual or threatened use of a weapon, sale or distribution of a controlled substance, or its possession with intent to distribute.
h) Death or incapacitation.

Section 8. A notice shall be sent to the member, using the last address on file, setting forth the expulsion and the reasons therefore. Such notice shall be sent within fifteen days of the recommendation for termination. The Advisory Committee shall submit, in writing and within thirty days after sending the notice, a recommendation, a letter to the Executive Director of the department stating the Advisory Committee's recommendation for termination of membership. The member will be terminated by action of the Committee Chair and/or Executive Director.

ARTICLE V: Officers
Section 1. The elected officer of the Advisory Committee shall be the Chairperson:
(a) The Chairperson shall be an employee of CDPHE.
(b) The election shall be conducted within the first ninety days of the establishment of the Advisory Committee for the first year and annually at the first meeting held after June 30 in each calendar year in subsequent years.
(c) The Chairperson may be removed from office:
(I) At any time for cause the Advisory Committee may deem sufficient, by a vote of three-fourths of the entire voting membership present.
(II) Written notice giving time, place, and purpose of this meeting shall be mailed to each member of the Advisory Committee at least three working days prior to the meeting.
(III) If the Chairperson is removed at such meeting, an election for a successor shall take place at the same meeting.
Section 2. The term of office for the Chairperson shall be one year commencing at the close of the meeting at which they were elected.
Section 3. A vacancy in office shall exist in the event of the Chairperson's death, resignation, or removal from office.
Section 4. Duties of the Chairperson shall be to:
a) Preside at all meetings of the Advisory Committee;
b) Build and present meeting agendas ;
c) Observe and enforce the bylaws and policies of the Advisory Committee; and
d) Perform all such other duties of the office as provided by these bylaws or prescribed by the Advisory Committee.

Section 5. In the absence of the Chairperson at any meeting in which a quorum is present, the members present shall elect a Chairperson to serve for that meeting only.

ARTICLE VI: Department Staff
Section 1. The Advisory Committee shall be supported by select department staff, and/or designees.
Section 2. Duties of the department staff, and/or designees, responsible for assisting the committee shall be:

a) Provide support to the scientific processes of the Advisory Committee;
b) Prepare meeting documents under the direction of the Chairperson, consistent with state and department rules;
c) Ensure background documents are prepared and information is presented to support the work of the Advisory Committee;
d) Attend and present designated materials to members of Advisory Committee at meetings.

Section 3. The coordinator, in collaboration with the Advisory Committee, shall:
a) Notify all Advisory Committee members and announce to the public, the time and place of the Advisory Committee meetings at least seven working days prior to such meetings;
b) Assist the Chairperson in the planning of meetings and development of agendas;
c) Record, maintain, and distribute accurate minutes of all Advisory Committee meetings.
d) Attend to official correspondence
e) Maintain the official Colorado Department of Public Health and Environment Retail Marijuana website;
f) Serve as a liaison to the Chairperson through participation in meetings, conference calls and emails;
g) Assists in the development and handling of the final recommendations of the Committee to the department.

ARTICLE VII: Meetings
Section 1. The Advisory Committee shall meet at once monthly.
Section 2. A minimum quorum of nine members shall be required for all decisions of the Advisory Committee;
a) No proxy or absentee voting shall be allowed;
b) Members may fully participate in a meeting via teleconference;
c) Any meeting may be cancelled by the Chairperson a minimum three working days prior to such meeting, when, in consultation with coordinator and/or department staff, the Chairperson determines the meeting is not needed, or when there will not be a quorum present.
d) Any meeting may be cancelled by the Chairperson at any time due to inclement weather or an emergency situation.

Section 3. In absence of a quorum, any business transacted is null and void, except to take measures to obtain a quorum or to reschedule another meeting.
Section 4. All meetings of the Advisory Committee shall be open to the public in accordance with regulations of the Colorado Open Records Act and Sunshine Law. The Advisory Committee may move to Executive Session in accordance with the Open Records Act. Notice of all meetings shall be posted on the Retail Marijuana program's web site.
Section 5. All decisions and recommendations from the Advisory Committee to the department, Board of Health, or other state entity shall have been adopted by majority vote of the Advisory Committee.
Section 6. No individual member shall make a statement of policy that purports to be that of the Advisory Committee unless the Advisory Committee shall have adopted such policy, but no one shall be prohibited from stating his or her personal opinions, provided they are clearly identified as such.

Section 7. All discussions of the Advisory Committee relative to the work of the committee are regarded as confidential information, not to be discussed in any form outside the context of the Advisory Committee meetings.

ARTICLE VIII: Subcommittees and Task Forces
Section 1. Subcommittees of the Advisory Committee may be established as needed by majority vote of the Advisory Committee.
Section 2. Ad hoc committees and task forces including other individuals, groups, organizations or associations, pursuant to Article III, may be established by majority vote at any meeting of the Advisory Committee:
   a) Membership shall be prescribed by the Advisory Committee;
   b) The Advisory Committee shall appoint the chairpersons of ad hoc committees and task forces; that chairperson shall come from Advisory Committee membership;
   c) Ad hoc committees shall be given prescribed purposes and prescribed dates of discontinuance.

Section 3. Meetings of the subcommittees and any ad hoc committee or task force shall be open to the public, and shall hear testimony from the public in attendance in a manner as prescribed by the Advisory Committee:
   a) Meetings shall be at the call of the Chairperson of the subcommittee or task force.
   b) Meetings shall be announced at least seven working days prior to the meeting date in a manner as prescribed by the Advisory Committee.
   c) A majority of the current membership of Advisory Committee subcommittees or any ad hoc committee or task force shall constitute a quorum.
   d) No proxy or absentee voting shall be allowed for any member of a subcommittee or task force; however, a subcommittee member may fully participate and vote by teleconference;
   e) In the absence of the subcommittee or task force chairperson, the members shall elect a chairperson who shall serve for that meeting only.
   f) Meetings of Advisory Committee subcommittees, ad hoc committees, and task forces shall be conducted in the manner as prescribed in the parliamentary authority.
   g) Minutes of all subcommittee meetings shall be made, copies of which shall be remitted to the members of the subcommittee and the Advisory Committee.

ARTICLE IX: Voting and Balloting Procedures
Section 1. In any instance in which a majority vote is called for, the Chairperson or coordinator shall issue a call for a voice vote, show of hands, or a secret ballot consisting of pieces of paper on which the member prints his or her choice.
   a) No proxy or absentee voting shall be allowed.

Section 2. If no issue receives a majority of the votes cast, another vote shall be taken.
Section 3. All committee members, including the Chairperson, shall have voting rights.

ARTICLE X: Parliamentary Authority
Meetings shall be conducted generally in keeping with Robert's Rules of Order, but shall be as informal as circumstances permit.
ARTICLE XI: Adoption of Bylaws
These Bylaws shall take effect immediately upon majority vote of the Advisory Committee.

ARTICLE XII: Amendment of Bylaws
Section 1. The Bylaws may be amended in whole or in part at a meeting of the Advisory Committee:

a) By three-fourths vote provided that such amendment was submitted to the Advisory Committee at least ten working days prior to the meeting at which such amendment is to be offered and remitted to all members of the Advisory Committee.
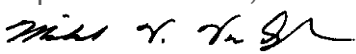
Section 2. Adopted amendments shall take effect immediately upon adoption.

ARTICLE XIII: Conflict of Interest
Section 1. Where a personal, professional, or financial conflict of interest may exist, participation by members of the Advisory Committee, including engaging in tasks or duties of the Advisory Committee, shall be determined under this Section.

a) A conflict of interest means engagement in an official act or recommendation of the Advisory Committee, which may be influenced by a real or perceived, direct benefit from an enterprise in which the member has a direct interest. A conflict of interest may also exist in circumstances where the member has a personal or professional interest that would interfere with participating objectively in an official act or recommendation.

b) All members must complete a Biographical Data, Conflict of Interest and Disclosure form prior to voting on any specific public health recommendation. This form will be publicly available.

c) A member must disclose the conflict of interest, before the discussion begins or as soon thereafter as the conflict is perceived, and disclose to the Advisory Committee the basis of the conflict. The member can then either disqualify him or herself from any further participation or voting on the matter at hand, or upon disclosure of the conflict, the Chairperson will ask for comments from any members or any member of the public present. Except for the member disclosing the potential conflict of interest, the Advisory Committee shall vote on whether a conflict of interest exists, and the member disclosing the potential conflict of interest shall be bound by the Advisory Committee's vote.

d) If a conflict is found to exist, the member disclosing the conflict of interest may be disqualified from discussion and/or voting on the matter at hand depending on the degree of conflict of interest. Conflicts of interest may include, but not be limited to, a committee member or his/her organization having a direct financial benefit in the matter at hand.

e) A conflict of interest may also be raised by other Advisory Committee members or any member of the public in attendance.

f) Any member wishing to abstain from voting shall notify the Advisory Committee according to the Advisory Committee's procedural policy mentioned above.

g) Any Advisory Committee member wishing to disengage from a required task or duty of the Advisory Committee shall notify the Advisory Committee and give citation of possible conflict of interest to the Chairperson.

h) Dispensation from voting or duty shall pertain only to the specified vote or duty.

Bylaws adopted on June 16, 2014

Signed: _Mike V. Van Dyke_
Mike Van Dyke, Committee Chair

Tri-County Health Department Women, Infant, and Children (WIC)

Marijuana Use Survey Results

COLORADO
Department of Public
Health & Environment

TO: Michael VanDyke, PhD
      Section Chief, Environmental Epidemiology
      Chair, Retail Marijuana Public Health Advisory Committee
      Colorado Department of Public Health and Environment

FROM: Christine Demont-Heinrich, MPH
      Population Health Epidemiologist

      Bernadette Albanese, MD, MPH
      Medical Epidemiologist
      Tri-County Health Department

SUBJECT: Overview of survey results regarding marijuana use among Women Infant and
      Children (WIC) Clients

DATE: December 16, 2014

Introduction

More than half of babies born in the United States participate in the Special Supplemental Nutrition
Program for Women Infant and Children (WIC). Tri-County Health Department (TCHD), Colorado's
largest local health department serving more than 26% of the state's population, has an average
monthly caseload of approximately 25,000 WIC clients. Colorado was the first state to legalize marijuana
in January 2014. Related to this new legislation, Tri-County Health Department conducted a survey of
WIC clients to assess marijuana use and to gain understanding regarding the educational needs around
health effects of marijuana use.

Survey Methodology

TCHD, along with the assistance from the Colorado Department of Public Health and Environment,
designed a voluntary, anonymous, in-person survey to learn about the needs and concerns that WIC
clients had regarding the health effects of marijuana and measure usage rates. The survey was web-
based using SurveyMonkey® and was administered in English and Spanish using iPads. The iPads were
rotated to all of the 10 TCHD WIC offices for a period of two weeks per clinic starting August 4 and
finishing October 10, 2014. Two additional satellite clinics also administered the survey during this time
period for two days each. Eligible WIC clients were asked to take the survey after their routine
appointment and represented a convenience sample for each clinic site. For eligibility, the client had to
be an endorser on the WIC program, be 18 years of age or older, and be able to independently take the
survey in English or Spanish using the iPad. A WIC endorser is a person or persons who represent the
WIC participant(s) in qualifying them for eligibility; must be the participant, a parent, legal guardian or
caretaker.

Serving Adams, Arapahoe and Douglas Counties ▼ www.tchd.org
6162 S. Willow Drive, Suite 100 ▼ Greenwood Village, CO 80111-5114 ▼ 303-220-9200

Appendix: Monitoring Health Concerns Related to Marijuana in Colorado: 2014   A-9
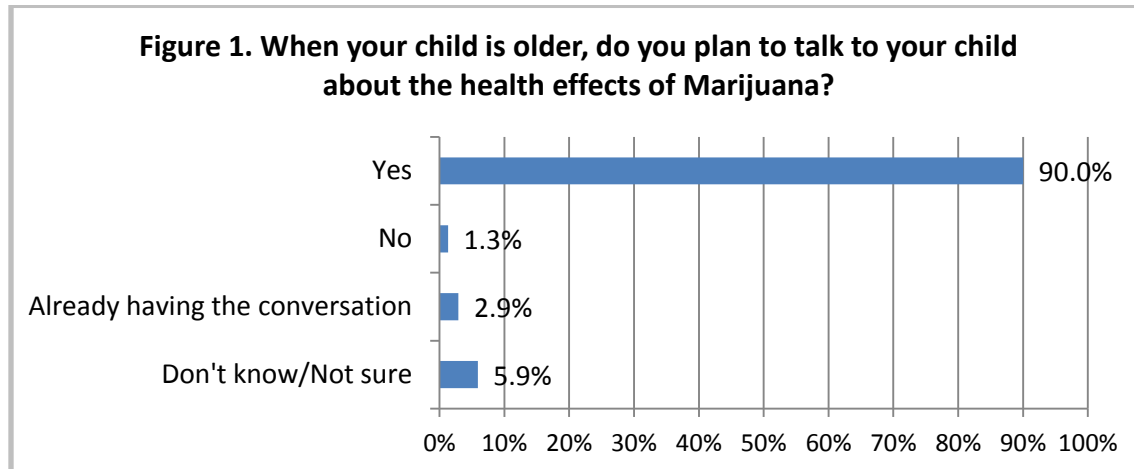
Results

Survey respondents: During the ten week administration of the survey, 3,137 clients had an on-site WIC appointment at the TCHD primary or satellite WIC clinics. Two hundred thirty-four clients (7.4%) were ineligible to take the survey based on criteria defined above. The remaining clients were asked to take the survey, and 1,749 were completed resulting in an overall 60.2% response rate. Among the 1,749 respondents, 1,308 (74.8%) surveys were completed in English and 441 (25.2%) were completed in Spanish.

Demographics: Table 1 shows the demographic characteristics of the WIC clients who participated in the survey. A high percentage of respondents were between the ages of 21 to 25 or 26 to 30 years. The majority of clients who took the survey identified as being the mother (87.6%) to the child or children on WIC.

Table 1. Demographic Profiles of survey respondents

Age Group	
18-20 years	10.1%
21-25 years	27.0%
26-30 years	25.4%
31-35 years	20.8%
36-40 years	11.7%
Over 40 years	5.0%
Gender	
Female	95.9%
Male	4.1%
Race/Ethnicity	
Non-Hispanic Origin	
White	29.4%
Black or African American	10.1%
Asian, Native Hawaiian or Other Pacific Islander	3.6%
Other Race or Multiracial	2.6%
Hispanic (of any race)	54.3%
Relationship to child on WIC	
Mother	87.6%
Pregnant and no other children on WIC	6.6%
Father	3.3%
Grandparent	0.9%
Guardian	0.5%
No children on WIC	0.3%
Other	0.8%

Educational needs: The majority of respondents (92.9%) reported that they plan to talk to their child or are already talking with their child about health risks of marijuana (Figure 1).

Figure 1. When your child is older, do you plan to talk to your child about the health effects of Marijuana?

Response	Percent
Yes	90.0%
No	1.3%
Already having the conversation	2.9%
Don't know/Not sure	5.9%

Twelve additional questions were asked to find out which type of educational needs regarding the health effects of marijuana WIC clients were interested in learning more about (Figure 2). The question that yielded the highest 'yes' responses was to learn more about the health effects of marijuana on children (54.7%).

Figure 2. Percent of WIC clients responding 'yes' to Marijuana education questions

Topic	Percent
Health effects of MJ on children	54.7%
Medical vs. Recreational MJ	53.7%
MJ active in body	52.8%
MJ use on parenting	50.3%
MJ effects on driving	50.2%
Types of MJ products	49.9%
Health effects of MJ on adults	49.0%
MJ addiction	47.1%
MJ use and breastfeeding	42.2%
MJ use and pregnancy	41.5%
Quit using MJ	28.2%

Marijuana use: After the education and demographics questions, the remaining survey questions asked WIC clients about their own marijuana use. Overall, 510 (31.0%) of survey respondents reported having ever tried marijuana. Figure 3 shows the breakdown of ever using marijuana by race/ethnicity, with higher usage reported from whites and other races.

Figure 3. Ever Tried Marijuana by Race/Ethnicity
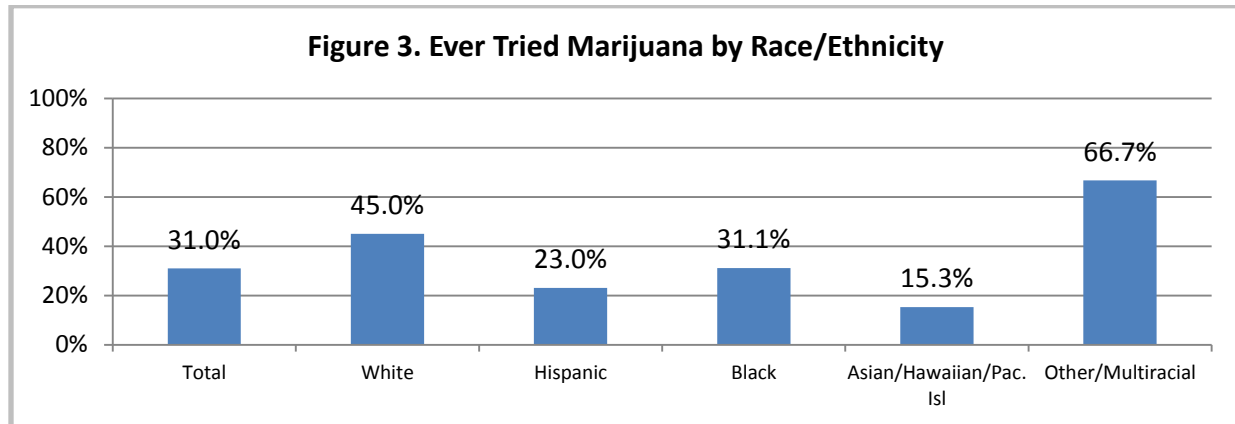
Marijuana use among WIC mothers: Since the far majority of survey respondents were mothers or pregnant mothers receiving WIC services (N=1,616; 92%), the remainder of the marijuana use analysis focused just on those clients.

1) Ever, past, and current marijuana users among WIC mothers: This subset of women was further classified into three use categories – ever, current, and past users. Ever users reported any previous use of marijuana. Current users were as having used marijuana at least once during the past 30 days. Past users were mothers who ever used marijuana, but had not used within the past 30 days. Among WIC mothers:
   - 29.1% (470) ever used marijuana
   - 5.9% (95) currently used marijuana
   - 23.2% (375) used marijuana in the past

   In this survey, the majority of WIC mothers who reported using marijuana were aged 30 years and younger (Table 2). The prevalence of marijuana use among WIC mothers who were 30 years of age and younger was consistently higher than use among older mothers (Table 3).

Table 2. Age group breakdown of WIC mothers who were ever, current, or past marijuana users

Survey respondents - WIC mothers	Aged ≤30 years [¶] % (#)	Aged >30 years [¶] % (#)
Ever users (N=470)	72.6% (341)	27.4% (129)
Current users (N=95)	76.8% (73)	23.2% (22)
Past users (N=375)	71.5% (268)	28.5% (107)

[¶] Percent of WIC mothers in the marijuana user group

Table 3. Proportion of WIC mothers by age who were ever, current, or past marijuana users

Survey respondents - WIC mothers	Ever users[¶][§] % (#)	Current users[¶] % (#)	Past users[¶][§] % (#)
WIC mothers < 30 years (N=992)	12.0% (119)	7.4% (73)	4.6% (46)
WIC mothers > 30 years (N=544)	5.7% (31)	4.0% (22)	1.7% (9)

[¶] Percent of WIC mothers in the age group

[§]Statistically significant difference between older and younger WIC mothers

1) <u>Timing of marijuana use related to most recent pregnancy, breastfeeding or since baby was born:</u> Among those WIC mothers who reported ever using marijuana, a question was asked regarding when marijuana was used relative to her most recent pregnancy. The time periods were: prior to being pregnant; during the pregnancy; since the baby was born; and while breastfeeding. Results are summarized in Table 4. While the prevalence varied somewhat among ever, current, and past users, a consistent pattern was observed in that mothers reported substantially less marijuana use while breastfeeding as compared to during and after the pregnancy (unrelated to breastfeeding). Overall, WIC mothers who were current users reported substantially higher use of marijuana during any pregnancy-related time period.

Table 4. Timing of marijuana use during most recent pregnancy among ever, current, or past marijuana users

Survey respondents - WIC mothers	Ever users[¶] % (#)	Current users[¶] % (#)	Past users[¶] % (#)
Used marijuana during pregnancy	10.9% (51)	35.8% (35)	4.5% (17)
Used marijuana since the baby was born	9.6% (45)	41.1% (39)	1.6% (6)
Used marijuana while breastfeeding	3.0% (14)	13.7% (13)	<1% (1)

[¶] Percent of WIC mothers in the marijuana user group; N=470 ever users; N=95 current users; N=375 past users.

2) <u>Reasons for using marijuana:</u> WIC mothers who reported ever using marijuana were also asked the reason they used and results are summarized in Table 5. Respondents could choose more than one response. Among current users, the most common reasons reported were to help with depression/anxiety/stress and to help with pain. However, ever and past users commonly reported using marijuana for fun/recreation.

Table 5. Reason for marijuana use [§]

Survey respondents - WIC mothers	Ever users % (#)	Current users % (#)	Past users % (#)
To help with depression/anxiety/stress	35% (164)	63% (60)	28% (103)
To help with pain	29%(135)	60% (57)	21% (78)
To help with nausea/vomiting	23% (108)	48% (46)	17% (62)
For fun/recreation	59% (277)	39% (37)	65% (240)
Other reason	16% (75)	14% (13)	16% (58)

[§]Other reasons (write in response) included: sleep, cancer, seizures, migraines, and increase appetite. A couple of direct quotes from respondents were:
"To help with nausea and vomiting in first trimester of pregnancy"
"All the reasons above and plus when I was pregnant, it helped me want to eat."

3) <u>Estimates of marijuana use during pregnancy and the manner in which marijuana was used:</u>
Fifty-one WIC mothers reported using marijuana during their most recent pregnancy (35.8% of current users and 4.6% of past users). Among these 51 women, the manner in which marijuana was used included:
- 96% smoked
- 51% consumed via food or beverage
- 41% vaporized

Key Survey Findings

- Overall prevalence of ever using marijuana among WIC mothers was 29.1%.
- Overall prevalence of current marijuana use among WIC mothers was 5.9%.
- Marijuana use was correlated with age, with the majority of marijuana users aged 30 years and younger.
- Marijuana use was also correlated with race and ethnicity, with a higher percentage of white, non-Hispanics using marijuana compared to Hispanics (despite a higher percent of survey respondents being Hispanic).
- Current marijuana users regularly used marijuana during and after pregnancy (35.8% and 41.1%, respectively); however, current users reported much less use while breastfeeding (13.7%). Reasons for using marijuana among current users included depression, anxiety, stress, pain, nausea, and vomiting.
- WIC mothers who were past marijuana users reported substantially lower marijuana use during and after pregnancy as compared to current users.

Study Limitations

- Although overall survey response rate was high at 60.2%, the results are from a convenience sample of WIC clients visiting TCHD clinics over a several week period. Selection bias may have occurred among those women who agreed to participate in the study. Results may not be generalizable to the entire WIC population nor the general population.
- Recall bias may have occurred among women reporting past marijuana use, particularly for use related to a pregnancy. Behavior around current use may be more accurate than reported behavior from past use.
- Marijuana use may have been underreported by WIC women who had concerns about disclosing such behavior, even in an anonymous survey.
- The study did not specifically identify all WIC women who were currently pregnant (only those who were receiving WIC services because of pregnancy and not for other children). Estimates of marijuana use during pregnancy may be over or underestimated.

Healthy Kids Colorado Survey (HKCS)

Marijuana Overview (2013)

COLORADO
Department of Public
Health & Environment

The Healthy Kids Colorado Survey (HKCS) collects self-reported health information from Colorado middle and high school students. A unified version of the survey was launched in 2013 that consolidates multiple needs for youth health data and allows for both state and regional-level results. The unified HKCS was administered in Fall 2013 to over 40,000 middle and high school students.

This summary outlines findings from the marijuana-related items included in the 2013 HKCS high school survey. The survey was primarily administered before retail marijuana sales went into effect.

Marijuana Behaviors & Perceptions, High School

- Overall, 36.9% of Colorado high school students tried marijuana one or more times in their life (lifetime use).

- One-fifth (19.7%) of students reported using marijuana in the past 30 days (current use).

- Over half (54.9%) of students think that marijuana is easy/very easy to access.

- More than half (54.0%) of students think people risk harming themselves from using marijuana regularly.

- Overall, 86.4% of students think parents feel it is wrong/very wrong for the student to use marijuana.

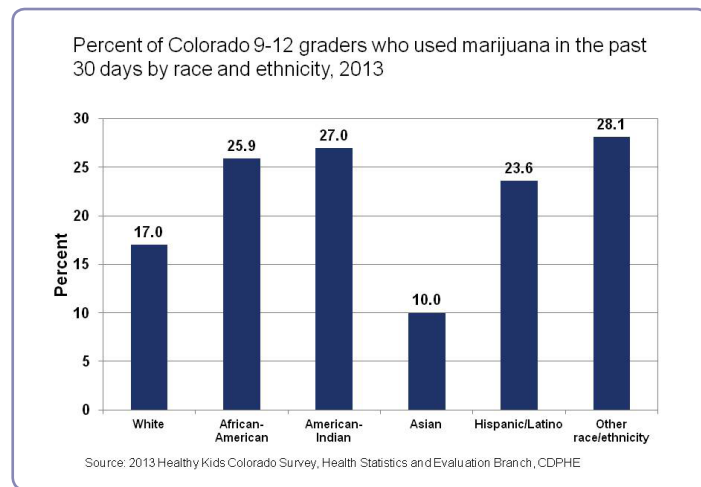- One-third (32.9%) think police would catch kids who used marijuana in the student's neighborhood.

- A total of 8.1% of Colorado high school students tried marijuana before age 13.

- Over one-tenth (10.9%) of students who drove during the past 30 days reported driving one or more times when they had been using marijuana.

- A total of 5.2% of students used marijuana on school property in the past 30 days.

- Overall, 60.2% of high school students think it is wrong/very wrong for kids the student's age to use marijuana.

- A total of 82.5% think adults feel it is wrong/very wrong for kids the student's age to use marijuana.

- Overall, 36.0% know someone with a Medical Marijuana License.

Trends for Marijuana Use, High School

- The trend for current and lifetime marijuana use has remained stable since 2005.

- Data has been collected related to marijuana use in the past 30 days (current use) and for lifetime use (ever used) between 2005-2013.

- The sample sizes from 2005-2011 ranged from about 700 to 1,500 students and the sample size for 2013 for current and lifetime use was about 25,000 high school students.

- The survey methodology changed in 2013 to include charter schools and to expand the sample size.

- Although the estimates for marijuana use are lower in 2013 than previous years, these estimates are within the margin of error and do not represent a statistically significant decrease between 2005-2013.

Marijuana Use by Race/Ethnicity, Sex and Sexual Orientation, High School

The following charts present data comparing current marijuana use by race/ethnicity, sex and sexual orientation (students reporting as gay, lesbian or bisexual, i.e., GLB). Data by race/ethnicity and by sexual orientation were not available in previous years.

Percent of Colorado 9-12 graders who used marijuana in the past 30 days by race and ethnicity, 2013

Race/Ethnicity	Percent
White	17.0
African-American	25.9
American-Indian	27.0
Asian	10.0
Hispanic/Latino	23.6
Other race/ethnicity	28.1

Source: 2013 Healthy Kids Colorado Survey, Health Statistics and Evaluation Branch, CDPHE

APPLICATIONS OF HKCS DATA

These data are intended to create awareness about priority health behaviors of youth in Colorado, as well as to provide a tool to assess how behaviors change over time. Data can be used by key stakeholders, including legislators, educators, students, parents, community members and school staff to better understand behaviors, set program goals, develop programs, support health-related policies and seek funding.

In 2013, numerous schools and communities choose to participate in a local administration of the survey to be able to compare their results to state data and national data to better understand what priorities may exist in their community and to monitor health behavior trends. In 2013, over 200 schools participated in a state-administered HKCS, representing over 40,000 students.

An executive summary is available.

Percent of Colorado 9-12 graders who used marijuana in the past 30 days by sex and sexual orientation, 2013
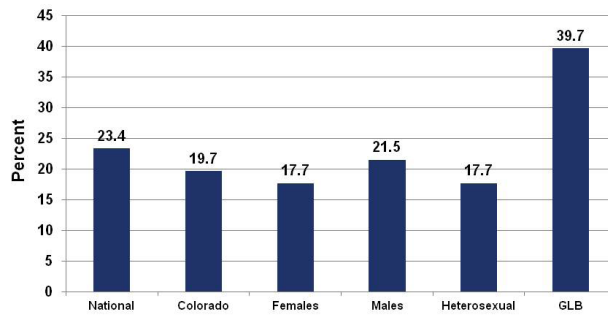
Source: 2013 Healthy Kids Colorado Survey, Health Statistics and Evaluation Branch, CDPHE

Additional Data and Comparisons

The high school survey also found that most students who use marijuana reported that they accessed marijuana by someone giving it to them (42.6%) while a smaller number took it from a family member (2.5%) or got it at school (4.2%). Most high school students who used marijuana smoked it (85.0%) while a smaller number ate it (5.2%) or vaporized it (6.2%).

Based on additional analysis of the 2013 high school HKCS data, students who felt they have someone who they could go to for help with a serious problem had significantly lower rates of current marijuana use. Also, students are more likely to use marijuana as they progress through high school, as shown in the chart below.

Percent of Colorado 9-12 graders who used marijuana in the past 30 days by grade level, 2013
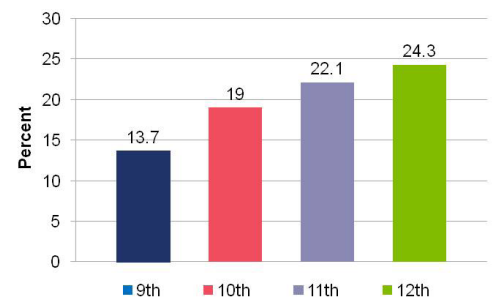
Source: 2013 Healthy Kids Colorado Survey, Health Statistics and Evaluation Branch, CDPHE

CONTACT

✉ ☎

Sarah Nickels, PhD, MSW

Colorado Dept. of Public Health and Environment

Healthy Kids Colorado Survey Project Lead

sarah.nickels@state.co.us

303-691-4043

www.healthykidscolo.org

Colorado Hospital Association Data, 2000-2014

Analysis Methods and Results

COLORADO
**Department of Public
Health & Environment**

CHA Data Analysis Methods

Marijuana Exposures, Diagnoses, and/or Billing Codes
To determine HD and ED visits that were possibly associated with marijuana, four ICD-9-CM diagnosis codes were used.

- E854.1 - Accidental poisoning by psychodysleptics (hallucinogens)
- 969.6 - Poisoning by psychodysleptics (hallucinogens)
- 305.2 - Nondependent cannabis abuse
- 304.3 - Cannabis dependence

For codes E854.1 and 969.9, psychodysleptics includes cannabis derivatives, lysergide (LSD), marihuana (derivatives), mescaline, psilocin, and psilocybin. The prevalence of use of other drugs in this category is low. Furthermore, E854.1 cannot be used as a primary diagnosis code but can be present with other marijuana related codes (969.6, 304.3, or 305.2). Reporting of code 969.6 must exclude codes 304.3 cannabis dependence and 305.2 nondependent cannabis abuse.

The differences in use of codes 305.2 (nondependent cannabis abuse) and 304.3 (cannabis dependence) in practice is unclear. Our conversations with hospital coders indicated that these codes may not be applied consistently from hospital to hospital. Therefore, our analyses only included HD and ED visits using these codes with HD and ED visits with all marijuana associated codes. HD and ED visits with possible marijuana exposure, diagnoses, or billing codes were determined by the presence of any of the four discharge codes. When examining HD and ED visits with marijuana exposures, only codes E854.1 and 969.6 were used. Each HD or ED visit with marijuana associated codes was counted once regardless of the number of marijuana associated codes listed.

Marijuana Legalization Eras
Rates of HD and ED visits were described over time by year. However, in order to evaluate the impact of changes in marijuana laws in Colorado, four marijuana legalization eras were chosen to display these findings.

- 2000 – Prior to Legalized Medical Marijuana
- 2001-2009 – Medical Marijuana Legalized
- 2010-2013 – Medical Marijuana Commercialized
- 2014 – Retail Marijuana Legalized

Analysis Population
In order to quantify the CHA data graphically and statistically test the differences across marijuana eras, the data was broken into four study populations: (1) HD from 2000 to 2013, (2) HD from January through June 2000 to 2014, (3) ED visits from 2011 to 2013, and (4) ED visits from January through June 2011 to 2014. All analyses are subsets of the following four analysis populations.

(1) There were 6,674,615 HD from 2000 to 2014. Of those, 64,246 (1.0%) were HD with possible marijuana exposures, diagnoses, or billing codes (discharge codes E854.1, 969.6, 304.3, or 305.2). We excluded 72 HD with possible marijuana exposures, diagnoses, or billing codes because codes 304.2 and 305.2 were both reported. The final analysis population included 6,674,543 HD (99.9%). In this population 565 (0.008%) HD were missing gender, 120,352 (1.8%) HD were missing race/ethnicity, and 2,074,798 (31.1%) HD were missing county of residence. (2) This population was then restricted to only HD in January through June of

each year. There were 3,596,918 HD in January through June of each year from 2000 to 2014. Of those there were 36,862 (1.0%) HD with possible marijuana exposures, diagnoses, or billing codes. Six HD were excluded for having both discharge codes 304.3 and 305.2 reported. The final analysis population included 3,596,912 (99.9%) HD. In this population 271 (0.007%) HD were missing gender and 60,673 (1.7%) HD were missing race/ethnicity. This population was not examined at the county level.

(3) There were 4,403,910 ED visits from 2011 to 2013. Of those 32,331 (0.7%) were ED visits with possible marijuana exposures, diagnoses, or billing codes (discharge codes E854.1, 969.6, 304.3, or 305.2). Four ED visits were excluded for having both discharge codes 304.3 and 305.2 reported. The final analysis population included 4,403,906 ED visits. In this population 1,048 (0.02%) ED visits were missing sex and 4,265 (0.1%) ED visits were missing race/ethnicity. The county level was not examined for ED visits with possible marijuana exposures, diagnoses, or billing codes because there was not a previous time period for comparison. (4) This population was then restricted to only ED visits in January through June of each year. There were 3,103,204 ED visits in January through June of each year from 2011 to 2014. Of those 25,186 (0.8%) were ED visits with possible marijuana exposures, diagnoses, or billing codes. One ED visit was excluded for having both discharge codes 304.2 and 305.2 reported. The final analysis population included 3,103,203 (99.9%) ED visits. In this population 692 (0.02%) ED visits were missing gender and 3,896 (0.1%) ED visits were missing race/ethnicity. This population was not examined at the county level.

First, we investigated rates of HD and ED visits with possible marijuana exposures and diagnoses by restricting the four populations to HD and ED visits with discharge codes E854.1 and 969.6 in patients younger than 9 years old (Figure 1), and in patients 9 years old or older (Figure 2) across marijuana legalization eras. Numbers of HD and ED visits with possible marijuana exposures and diagnoses were mapped by county for children under 9 years old from 2004 to 2013 (Map 1). Then the four populations were restricted to only HD and ED visits with marijuana associated codes (discharge codes E854.1, 969.6, 304.3, and 305.2) in the first three listed discharge codes and rates of HD and ED visits were examined by year and by marijuana legalization era (Figure 3 and 4). We hypothesized that marijuana associated codes within the first three discharge codes were more likely to reflect HD or ED visits possibly due to marijuana exposures or diagnoses. Then we broadened our scope and examined the four described populations by rates of HD and ED visits with marijuana associated discharge codes (discharge codes E854.1, 969.6, 304.3, and 305.2) in any of the listed discharge codes across years and marijuana legalization eras (Figure 5 and 6). These rates were stratified by gender (Figure 7), age (Figure 8), race/ethnicity (Figure 9), and county (Map 2 and 3).

Demographic Variables
Gender: The data was stratified by males and females to examine differences. HD and ED visits with missing gender were excluded from the statistical analysis.

Age: Age categories were developed using previous marijuana literature and recommendations made by the Retail Marijuana Public Health Advisory Committee. Age was divided into 6 categories: Children (<9 years), Adolescents (9-17 years), Young Adults (18-25 years), Adults (26-34 years), Middle Aged (35-64 years), and Elderly (≥ 65 years). Nine years was chosen as a cut off age for children because children under 9 years of age are not likely intentionally using marijuana and possible marijuana exposures are more likely accidental. There no HD or ED visits missing age.

Race/Ethnicity: Race and ethnicity were captured in one variable in the CHA database and are therefore mutually exclusive. Race and ethnicity categories were White, Black, Hispanic, Other, and Unknown. Other race included Asian, Native American, and Other. Unknown race was recorded as "unknown" not including missing data. HD and ED visits missing race/ethnicity were excluded from the stratified analysis.

County: CHA hospitalization data is geocoded from 2004 forward, and 2011 forward for ED data. Therefore, to examine rates of HD at the county level only two marijuana legalization eras could be mapped for HD and one for ED visits. We did not map ED visits because it could not be compared to a previous marijuana legalization era. However, counts of ED visits were combined with counts of HD when examining possible marijuana exposures (discharge codes E854.1 and/or 969.9) in children less than 9 years by county. HD and ED visits with missing county level data were excluded from the maps.

CHA Data Analysis Results
HD and ED Visits with Possible Marijuana Exposures in Children under 9 Years Old
Rates of HD remained constant from 2000-2009 and then began showing an increasing trend from 2010-2013 to January through June 2014. Rates of ED visits showed an increasing trend from 2011-2013 to January through June 2014. Rates of HD with possible marijuana exposures in children up to 9 years significantly increased from 2001-2009 to 2010-2013 from 1.2 to 7.6[1] by more than 5 fold. The highest rates for both HD and ED visits were in January to June of 2014 of 9.5 and 26.4 respectively. It is unclear whether the overall rates in 2014 will be increased from the previous time period. The reported rates of HD and ED visits for 2014 are for data from January through June of 2014 and the statistical test for difference from the previous time period is comparing January through June for each year in the 2010-2013 (2011-2013 for ED visits) time period to January through June in 2014. Though the rates of ED visits for January through June 2014 were not statistically significantly different from January through June 2011-2013, it was increased from 6.6 to 9.5 by 43.9%. Rates of HD for January through June 2014 were significantly increased from 6.2 to 26.4[2] by more than three fold; however, after adjusting for multiple comparisons this finding becomes marginally significant (Figure 1). Map 1 shows numbers of HD and ED visits with possible marijuana exposures in children up to 9 years old. Darker colored counties indicate higher counts while counties in white show no reported HD or ED visits with possible marijuana exposures in children up to 9 years. Higher numbers of HD and ED visits were in urban areas compared to rural areas. Counts of HD and ED visits with possible marijuana exposures were highest in Denver, Adams, and El Paso counties.

HD and ED Visits with Possible Marijuana Exposures in Patients 9 Years and Older
Rates of HD with possible marijuana exposures in patients 9 years and older significantly increased from 2001-2009 to 2010-2013 by 86.0% from 15 to 27.9[3]. The highest rates for both HD and ED visits were in January through June 2014 of 35.2 and 37.6 respectively. It is unclear whether the overall rates in 2014 will be increased from the previous time period. The reported rates of HD and ED visits for 2014 are for data from January through June of 2014 and the statistical test for difference from the previous time period is comparing January through June for each year in the 2010-2013 time period to January through June in 2014. Though the rates of HD for January through June 2014 were significantly increased from

---

[1] $(x^2(1, N=1,154,219)=22.7, p<0.0001)$
[2] $(x^2(1, N=633,602)=10.5, p=0.0012)$
[3] $(x^2(1, N=5,457,216)=91.8, p<0.0001)$

January through June 2010-2013 from 24.3 to 35.2 by 44.8%[4], after adjusting for multiple comparisons this finding becomes insignificant. However, rates of ED visits significantly increased from January to June 2011-2013 to January through June 2014 by 69.4% from 22.2 to 37.6[5] (Figure 2).

<u>HD and ED Visits with Possible Marijuana Exposures, Diagnoses, or Billing Codes in the First Three Diagnosis Codes</u>
Rates of HD and ED visits with possible marijuana exposures, diagnoses, or billing codes in the first three diagnosis codes remained constant from 2000 to 2009 and then showed an increasing trend from 2010 to January through June 2014. The highest increase in rates of HD was from 2009 to 2010 with an increase of 29%. For rates of ED visits the highest increase was from 2012 to 2013 and 2013 to January through June 2014 of 24% and 25% respectively (Figure 3). Rates of HD with possible marijuana exposures, diagnoses, or billing codes in the first three diagnosis codes by marijuana legalization eras showed a significant increase in rates from 289 to 373 by 29.1%[6] from 2001-2009 to 2010-2013 and from 362 to 515 by 42.3%[7] from January through June 2010-2013 to January through June 2014. Rates of ED visits with possible marijuana exposures, diagnoses, or billing codes in the first three diagnosis codes by marijuana legalization eras showed a significant increase in rates from 359 to 553 by 48.5%[8] from January through June 2011-2013 to January through June 2014. These findings support the increasing trend observed in rates of HD and ED visits across years. The highest rates of HD and ED visits were in January through June 2014 of 515 and 553 respectively (Figure 4).

<u>HD and ED Visits with Possible Marijuana Exposures, Diagnoses, or Billing Codes in Any of Listed Diagnosis Codes</u>
Rates of HD with possible marijuana exposures, diagnoses, or billing codes per 100,000 hospitalizations had an increasing trend from year 2000 to January through June 2014. The same increasing trend was observed in ED visits from year 2011 to January through June of 2014. However, rates of HD are higher than rates of ED visits overall. There was a 28.0% increase in rates of HD and a 27% increase in rates of ED visits with possible marijuana exposures, diagnoses, or billing codes from 2013 to January to June of 2014 (Figure 5). Rates of HD with possible marijuana exposures, diagnoses, or billing codes by marijuana legalization eras significantly increased from 2000 to 2001-2009 by 39.6% from 575 to 803[9], from 2001-2009 to 2010-2013 by 79.3% from 803 to 1,440[10], and from January through June 2010-2013 to January through June 2014 by 63.2% from 1,395 to 2,277[11]. Rates of ED visits significantly increased by 58.3% from January through June 2011-2013 to January through June of 2014 from 698 to 1,105[12]. The highest rates for both HD and ED visits were in January through June 2014 of 2,277 and 1,105 respectively (Figure 6).

Gender: For males, rates of HD with possible marijuana exposures, diagnoses, or billing codes significantly increased from 2000 to 2001-2009 by 35.7% from 887 to 1,204[13], 2001-2009 to 2010-2013 by 78.1% from 1,204 to 2,145[14], and January though June 2010-2013 to January

---

[4] $(x^2(1, N=2,932,283)=6.8, p=0.009)$
[5] $(x^2(1, N=2,579,518)=46.7, p<0.0001)$
[6] $(x^2(1, N=6,630,988)=297.9, p<0.0001)$
[7] $(x^2(1, N=3,576,906)=109.2, p<0.0001)$
[8] $(x^2(1, N=3,090,829)=565.2, p<0.0001)$
[9] $(x^2(1, N=6,674,543)=264.3, p<0.0001)$
[10] $(x^2(1, N=6,674,543)=5,122.6, p<0.0001)$
[11] $(x^2(1, N=3,602,185)=886.7, p<0.0001)$
[12] $(x^2(1, N=3,103,203)=1,256.8, p<0.0001)$
[13] $(x^2(1, N=2,729,936)=134.8, p<0.0001)$
[14] $(x^2(1, N=2,729,936)=3,063.5, p<0.0001)$

through June 2014 by 62.6% from 2,065 to 3,357[15]. Rates of ED visits significantly increased from January through June 2011-2013 to January through June 2014 by 52.7% from 1,011 to 1,544[16]. For females, rates of HD with possible marijuana exposures, diagnoses, or billing codes significantly increased from 2000 to 2001-2009 by 44.8% from 368 to 533[17], 2001-2009 to 2010-2013 by 75.0% from 533 to 933[18], and January though June 2010-2013 to January through June 2014 by 62.1% from 912 to 1,478[19]. Rates of ED visits significantly increased from January through June 2011-2013 to January through June 2014 by 67.4% from 457 to 765[20]. The highest rates of HD and ED visits were in January through June 2014 for both males and females. There are more HD and ED visits with possible marijuana exposures, diagnoses, or billing codes for males compared to females (Figure 7).

Age: Rates of HD and ED visits with possible marijuana exposures, diagnoses, or billing codes showed increasing trends across marijuana legalization eras across all ages. For children less than 9 years old, rates of HD significantly increased from 2001-2009 to 2010-2013 by more than three fold from 2 to 9[21]. For adolescents 9 to 17 years, rates of HD remained constant from 2000 to 2001-2009 and significantly increased from 2001-2009 to 2010-2013 by 47.4% from 4,348 to 6,411[22]. Rates of ED visits for adolescents remained constant from January through June 2011-2013 to January through June 2014. For young adults 18 to 25 years, rates of HD significantly increased from 2000 to 2001-2009 by 58.3% from 1,624 to 2,571[23], from 2001-2009 to 2010-2013 by 99.5% from 2,571 to 5,129[24], and January through June 2010-2013 to January through June 2014 46.0% from 4,995 to 7,291[25]. Rates of ED for young adults significantly increased from January through June 2011-2013 to January through June 2014 by 59.0% from 1,504 to 2,392[26]. For adults 26 to 34 years, rates of HD significantly increased from 2000 to 2001-2009 by 37.5% from 997 to 1,371[27], from 2001-2009 to 2010-2013 by 85.7% from 1,371 to 2,546[28], and January through June 2010-2013 to January through June 2014 56.9% from 2,465 to 3,867[29]. Rates of ED for young adults significantly increased from January through June 2011-2013 to January through June 2014 by 66.1% from 1,083 to 1,799[30]. For middle aged 35 to 64, rates of HD significantly increased from 2000 to 2001-2009 by 52.8% from 627 to 958[31], from 2001-2009 to 2010-2013 by 86.6% from 958 to 1,788[32], and January through June 2010-2013 to January through June 2014 87.6% from 1,758 to 3,298[33]. Rates of ED for middle aged significantly increased from January through June 2011-2013 to January through June 2014 by 68.4% from 659 to 1,110[34]. For elderly aged 65 and older, rates of HD significantly increased from 2001-2009 to 2010-2013 by more than three fold from 22 to 89[35] and from January through June 2010-2013 to January through June 2014 by more than two

---

[15] $(x^2(1, N=1,481,154)=540.9, p<0.0001)$
[16] $(x^2(1, N=1,356,331)=658.3, p<0.0001)$
[17] $(x^2(1, N=3,944,038)=125.4, p<0.0001)$
[18] $(x^2(1, N=3,944,038)=1,821.2, p<0.0001)$
[19] $(x^2(1, N=2,120,759)=325.1, p<0.0001)$
[20] $(x^2(1, N=1,746,144)=604.8, p<0.0001)$
[21] $(x^2(1, N=1,154,226)=22.8, p<0.0001)$
[22] $(x^2(1, N=192,741)=280.3, p<0.0001)$
[23] $(x^2(1, N=568,826)=123.9, p<0.0001)$
[24] $(x^2(1, N=568,826)=1,898.1, p<0.0001)$
[25] $(x^2(1, N=299,112)=118.7, p<0.0001)$
[26] $(x^2(1, N=440,352)=381.8, p<0.0001)$
[27] $(x^2(1, N=758,787)=47.1, p<0.0001)$
[28] $(x^2(1, N=758,787)=1,124.6, p<0.0001)$
[29] $(x^2(1, N=405,136)=145.7, p<0.0001)$
[30] $(x^2(1, N=476,116)=374.6, p<0.0001)$
[31] $(x^2(1, N=2,089,759)=139.0, p<0.0001)$
[32] $(x^2(1, N=2,089,759)=2,246.1, p<0.0001)$
[33] $(x^2(1, N=1,118,319)=637.4, p<0.0001)$
[34] $(x^2(1, N=1,029,082)=531.4, p<0.0001)$
[35] $(x^2(1, N=1,910,204)=344.5, p<0.0001)$

fold from 86 to 288[36]. Rates of ED for the elderly significantly increased from January through June 2011-2013 to January through June 2014 by more than double from 64 to 132[37] (Figure 8).

Race/Ethnicity: The highest rates of HD and ED visits were observed in Blacks and the lowest rates in Whites and other races. For Whites, rates of HD significantly increased from 2000 to 2001-2009 by 36.2% from 547 to 745[38], 2001-2009 to 2010-2013 by 78.9% from 745 to 1,333[39], and January through June 2010-2013 to January through June 2014 by 68.8% from 1,281 to 2,162[40]. Rates of ED visits for Whites also significantly increased from January through June 2010-2013 to January through June 2014 by 61.6% from 685 to 1,107[41]. For unknown race, rates of HD significantly increased from 2000 to 2001-2009 by 99.4% from 342 to 682[42], 2001-2009 to 2010-2013 by 84.2% from 682 to 1,256[43], and January through June 2010-2013 to January through June 2014 by 75.1% from 1,171 to 2,051[44]. Rates of ED visits for unknown race also significantly increased from January through June 2011-2013 to January through June 2014 by two fold from 616 to 1,846[45]. In Blacks, rates of HD significantly increased from 2000 to 2001-2009 by 26.2% from 1,710 to 2,159[46], 2001-2009 to 2010-2013 by 60.9% from 2,159 to 3,473[47], and January through June 2010-2013 to January through June 2014 by 25.9% from 3,378 to 4,254[48]. However, rates of ED visits for Blacks remained constant. In Hispanics, rates of HD significantly increased from 2001-2009 to 2010-2013 by 88.2% from 894 to 1,683[49] and January through June 2010-2013 to January through June 2014 by 65.5% from 1,675 to 2,772[50]. Like Blacks, rates of ED visits for Hispanics remained constant. For other races, rates of HD significantly increased from 2001-2009 to 2010-2013 by 20.4% from 941 to 1,133[51] and January through June 2010-2013 to January through June 2014 by 64.1% from 1,181 to 1,938[52]. Rates of ED visits for other races significantly increased from January through June 2011-2013 to January through June 2014 by 42.9% from 801 to 1,145[53] (Figure 9).

County: Map 2 shows the rates and numbers of HD with possible marijuana exposures, diagnoses, or billing codes. Darker colored counties indicate higher counts while white counties show no reported HD with possible marijuana exposures, diagnoses, or billing codes. Higher rates of HD were in urban areas compared to rural areas for both time periods 2004-2009 and 2010-2013. From 2004-2009 the highest rates of HD were in Denver, Custer, Pueblo, and Crowley counties (Map 2). In 2010-2013 rates increased in Adams, Clear Creek, Gilpin, Larimer, Crowley, Bent, Routt, Eagle, Pitkin, and Moffat counties from 2004-2009. The highest rates of HD in 2010-2013 were in Denver, Adams, Clear Creek, Gilpin, Larimer, Pueblo, and Crowley counties (Map 3).

---

[36] $(x^2(1, N=1,042,903)=163.5, p<0.0001)$
[37] $(x^2(1, N=370,571)=40.3, p<0.0001)$
[38] $(x^2(1, N=4,048,288)=119.4, p<0.0001)$
[39] $(x^2(1, N=4,048,288)=2,980.7, p<0.0001)$
[40] $(x^2(1, N=2,219,373)=683.7, p<0.0001)$
[41] $(x^2(1, N=1,947,617)=874.2, p<0.0001)$
[42] $(x^2(1, N=1,114,376)=157.2, p<0.0001)$
[43] $(x^2(1, N=1,114,376)=566.0, p<0.0001)$
[44] $(x^2(1, N=572,711)=73.7, p<0.0001)$
[45] $(x^2(1, N=265,509)=735.8, p<0.0001)$
[46] $(x^2(1, N=254,520)=11.7, p=0.0006)$
[47] $(x^2(1, N=254,520)=336.8, p<0.0001)$
[48] $(x^2(1, N=139,293)=17.3, p<0.0001)$
[49] $(x^2(1, N=755,465)=749.2, p<0.0001)$
[50] $(x^2(1, N=397,469)=94.9, p<0.0001)$
[51] $(x^2(1, N=381,000)=30.9, p<0.0001)$
[52] $(x^2(1, N=212,404)=60.5, p<0.0001)$
[53] $(x^2(1, N=282,844)=77.3, p<0.0001)$

Marijuana Use During Pregnancy and Breastfeeding

Evidence Summary

COLORADO
Department of Public
Health & Environment

Epidemiology of Marijuana use in Pregnancy:

- The National Survey on Drug Use and Health reported in 2012-2013, 4.9% of pregnant 15-44 year old women used marijuana in the past month.National Household Survey on Drug Use and Health (2003-2004), 10% of American women aged 15-44 years reported use of an illicit drug in the past month. Of pregnant women in the same age group, 4.6% reported any illicit drug use, 3.6% reported cannabis use.
- Schauberger 2014 (Prevalence of illicit drug use in pregnant women): 200 prenatal women in a private practice in Wisconsin had urine tests at intake- 7% positive for MJ. Only 4.5% of this sample self-reported ANY drug use, while 13% had a positive urine test for one or more drugs.
- Hayatbakhsh et al 2012: large cross-sectional study (24,874 women) at a tertiary public hospital in Australia (2000-2006)
  - 2.6% of women used cannabis during pregnancy (based on interview at 12-16 weeks of pregnancy)
- Moore 2010 (During pregnancy, recreational drug-using women. . . continued to smoke tobacco and cannabis): This study in the UK found that: among women who reported using marijuana in the month before getting pregnant, about ⅔ reported continued use after finding out they were pregnant, and throughout pregnancy, but at around half the volume.
- Fergusson 2002: Avon Longitudinal Study of Pregnancy and Childhood (UK), a large cohort study (12,129 women)
  - 4.8% of mothers self-reported smoking cannabis before pregnancy and 2.6% in 1st trimester, 2.1% in mid-pregnancy
- Saurel-Cubizolles MJ et al 2014: Cannabis use in France, 13,545 women
  - 1.2% of women reported cannabis use during pregnancy
    - 40% reported use less than once a month, 26% reported 1-9 times per month and 15% at least 10 times per month (19% didn't answer frequency question)

Birth Outcome Risks

Stillbirth

We found <u>limited</u> evidence that maternal use of marijuana during pregnancy is associated with an increased risk of stillbirth.
- Varner et al 2014 - Stillbirth Collaborative Research Network
  - *medium quality evidence based on strengths and limitations*
  - Findings:
    - Screening positive for tetrahydrocannabinolic acid was associated with an OR of 2.34 (95%CI 1.13-4.81, p=0.021) for stillbirth with partial confounding by cotinine (tobacco exposure).

- ○ Strengths:
  - ■ population based case-control study (March 2006-September 2008)
  - ■ 663 stillbirth deliveries (cases), 1932 live births (controls)
  - ■ sample was racially and ethnically diverse
  - ■ utilized maternal self-report + medical record review + toxicology screen
  - ■ Tested umbilical cord segments from both cases and controls for drugs including THC and obtained maternal blood samples
  - ■ adjusted for stillbirth risk factors at baseline using a modification to a risk factor score, including maternal characteristics: age,race/ethnicity, education, tobacco, alcohol, illicit drug use, comorbidities etc
- ○ Limitations:
  - ■ relatively small number of women tested positive for individual drugs and therefore lacked sample size to make definitive conclusions
  - ■ participants who did not have cotinine and toxicology testing differed in race, ethnicity and gestational age from those who had samples available for testing
  - ■ Unable to determine if exposure was before or after occurrence of stillbirth.

Preterm Delivery

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with preterm delivery.
- ● Day et al 1991: Maternal Health Practices and Child Development Study (Pittsburgh)
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ non significant relationship between prenatal marijuana use and prematurity
  - ○ Strengths:
    - ■ longitudinal study with large sample size (n=519 live born singleton births)
    - ■ quantified marijuana use and assessed use in each trimester
    - ■ study nurses were blinded to the exposure status of the infant
    - ■ adjusted for tobacco and alcohol use
  - ○ Limitations:
    - ■ no statistical data included in the paper to support the finding with regards to prematurity
    - ■ Inner city, outpatient clinic population with low socioeconomic status of women, 60% completed high school, 57% of population were black, 43% white
- ● Fergusson 2002: Avon Longitudinal Study of Pregnancy and Childhood (UK)
  - ○ *low quality of evidence based on strengths and limitations*
  - ○ Findings:

- No significant association between cannabis use before and during pregnancy and perinatal death, preterm delivery or need for special care admission of the newborn
  - ○ Strengths:
    - large cohort study (12,129 women) in UK
  - ○ Limitations:
    - cannabis use assessed by self-completion questionnaires mailed to mothers
    - the analysis for preterm delivery did not include an adjusted multivariate analysis
    - 70% of women who used cannabis also used tobacco, tobacco was adjusted for but unable to perform a stratified analysis of cannabis users only
- Hayatbakhsh et al 2012:
  - ○ *medium quality of evidence based on strengths and limitations*
  - ○ Findings:
    - Adjusted analysis: Significant association of cannabis use preterm birth (OR 1.5, 95%CI 1.1-1.9),
    - Using adjusted ORs, the population-attributable risk for preterm birth was 1.5%.
  - ○ Strengths:
    - large cross-sectional study (24,874 women) at a tertiary public hospital in Australia (2000-2006)
    - adjusted for multiple variables including cigarette smoking, alcohol and other illicit drug use
  - ○ Limitations:
    - self reported data on substance use
    - no quantification of amount of cannabis use during pregnancy
    - only looked at cannabis use at 1st prenatal visit (12-16 weeks)
    - potential inadequate confounding variables
- Dekker GA et al 2012 - Risk factors for preterm birth
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - Use of marijuana pre-pregnancy was an independent risk factor for spontaneous preterm birth (birth <37 weeks gestation) with intact membranes (OR 2.34, 95% CI 1.22-4.52)
  - ○ Strengths:
    - large prospective multicenter cohort of 3234 nulliparous women with singleton pregnancies (November 2004-August 2008)
  - ○ Limitations:
    - only looked at pre-pregnancy marijuana use, many women stop using during pregnancy and rates of use are not likely the same
    - study conducted in New Zealand and Australia, potentially limiting generalizability of findings.

- Bada HS et al 2005 - prenatal drug exposure and LBW/preterm births
  - *low quality evidence based on strengths and limitations*
  - Findings:
    - The preterm group had significantly higher proportions of mothers who used cocaine, opiates or marijuana during pregnancy
    - In the adjusted analysis for risk factors associated with prematurity, marijuana was not significantly associated (OR 0.9, 95%CI 0.73-1.11)
  - Strengths:
    - secondary data analysis from a large multicenter study (Maternal Lifestyle Study (4 centers of the National Institute of Child Health and Human Development Neonatal Research Network) - recruitment May 1993-May 1995
    - adjusted for tobacco, alcohol and other drug use, prenatal care, maternal medical risk factors
  - Limitations:
    - 16,988 mother/child dyads met eligibility criteria, only 70% were consented (11,811)
    - large percentage of Medicaid patients (64.2%), 43.4% of mothers were black, 29.3% had education <12 years, 34% had no/intermediate prenatal care
    - unable to determine the effect of each prenatal drug exposure independent of other substance exposures
- Shiono PH et al 1995 - Cocaine and MJ effect on LBW and preterm birth
  - *medium quality evidence based on strengths and limitations*
  - Findings:
    - 11% of women had THC-COOH in serum or self-reported using marijuana
      - 7.8% had positive serum
      - 5.6% had positive self-report
      - 2.4% had positive serum and positive self-report
    - No significant association with marijuana use and preterm birth (OR 1.1, 95%CI 0.8-1.3) or abruptio placentae (OR 1.3, 95%CI 0.6-2.8)
  - Strengths:
    - prospective multicenter cohort study in US
    - large multi-ethnic sample - 7470 women enrolled (43% African American, 24% Hispanic, 33% white or other)
    - interviewed women at 23-26 weeks gestation about risk factors
    - serum collected at study entry and also for a randomly selected subsample of 12% of women at 31-36 weeks gestation (3rd trimester)
      - serum tested for THC-COOH, any positive sample was confirmed by gas chromatography-mass spectrometry
    - adjusted for tobacco smoking
  - Limitations:
    - study conducted 1984-1989

- drug use categorized as yes/no variable
- no adjustment for alcohol use as described
- Saurel-Cubizolles MJ et al 2014: Cannabis use in France and preterm birth, small for gestational age
  - *low quality evidence based on strengths and limitations*
  - Findings:
    - 1.2% of women reported cannabis use during pregnancy
      - 40% reported use less than once a month, 26% reported 1-9 times per month and 15% at least 10 times per month (19% didn't answer frequency question)
    - Preterm (before 37 weeks) birth rate higher in cannabis users (10.9%) than non-users (5.3%)
      - For births before 32 weeks (1.3% for cannabis users and 0.5% in non-users)
    -
      - Preterm birth rate in users (using less than once per month) 9.9%
      - Preterm birth rate in users (using >1 time per month) 12.3%
    - adjusted OR for cannabis users who were non-tobacco smokers was non-significant for cannabis use less than once per month and preterm birth (OR 1.24, 95% CI 0.44-3.49)and small for gestational age
    - adjusted OR for cannabis users who were tobacco users was statistically significant for preterm birth (OR 2.68, 95%CI 1.16-6.20) and spontaneous preterm birth (OR 3.50, 95%CI 1.28-9.58)
  - Strengths:
    - Large sample size (13,545 women), national sample in France
    - Analyzed tobacco smokers and non-tobacco smokers separately
  - Limitations:
    - self-report of drug use
    - Interview done after delivery, could cause recall bias
    - Small percentage of cannabis users in the sample (1.2%)
    - limited sample size of cannabis-only users who used more than once per month - didn't allow for analysis of this group
    - large confidence intervals

Low Birth Weight (birth weight <2500g regardless of gestational age)

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with low birth weight infants.
- Hayatbakhsh et al 2012:
  - *medium quality of evidence based on strengths and limitations*
  - Findings:
    - 2.6% of women used cannabis during pregnancy (based on interview at 12-16 weeks of pregnancy)
    - Adjusted analysis: Significant association of cannabis use with low birth

weight (OR 1.7, 95%CI 1.3-2.2)
- ■ Using adjusted ORs, the population-attributable risk for low birth weight, was 2.5%.
  - ○ Strengths:
    - ■ large cross-sectional study (24,874 women) at a tertiary public hospital in Australia (2000-2006)
    - ■ adjusted for multiple variables including cigarette smoking, alcohol and other illicit drug use
  - ○ Limitations:
    - ■ self reported data on substance use
    - ■ no quantification of amount of cannabis use during pregnancy
    - ■ only looked at cannabis use at 1st prenatal visit (12-16 weeks)
    - ■ potential inadequate confounding variables
- ● Schempf et al 2008
  - ○ *medium quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Unadjusted OR for marijuana use and low birth weight: OR 1.94, 95% CI 1.23-3.06, when adjusted for other drug use and social, psychosocial, behavioral and biomedical factors OR decreased to 1.07, 95%CI 0.60-1.92 (non-significant)
  - ○ Strengths:
    - ■ large sample (808 women with singleton, live births)
    - ■ Drug use measurement: universal urine toxicologic screen at admission to L&D, self-report or report in the medical record
    - ■ conducted sensitivity analyses with no change in drug effect
    - ■ adjusted for social, psychosocial, behavioral (tobacco and alcohol use, early prenatal care) and biomedical factors (hypertensive disorders, STIs, medical risk factors etc)
  - ○ Limitations:
    - ■ retrospective cohort study of low income women who delivered at Johns Hopkins (1995-1996)
    - ■ possible over-adjustment of factors
    - ■ did not assess for differences in gestational age
    - ■ 63% of the sample did not have early prenatal care (1st visit within the 1st trimester with 4 or more total visits)
- ● Bada HS et al 2005 - prenatal drug exposure and LBW/preterm births
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ The LBW and IUGR groups had significantly higher proportions of mothers who used cocaine, opiates or marijuana during pregnancy
    - ■ In the adjusted analysis for risk factors associated with LBW (OR 1.21, 95%CI 0.9-1.61) and IUGR (OR 1.08, 95%CI 0.85-1.36), marijuana was not statistically significant
  - ○ Strengths:

- secondary data analysis from a large multicenter study (Maternal Lifestyle Study (4 centers of the National Institute of Child Health and Human Development Neonatal Research Network) - recruitment May 1993-May 1995
- adjusted for tobacco, alcohol and other drug use, prenatal care, maternal medical risk factors
  - ○ Limitations:
    - 16,988 mother/child dyads met eligibility criteria, only 70% were consented (11,811)
    - large percentage of Medicaid patients (64.2%), 43.4% of mothers were black, 29.3% had education <12 years, 34% had no/intermediate prenatal care
    - unable to determine the effect of each prenatal drug exposure independent of other substance exposures
- Shiono PH et al 1995 - Cocaine and MJ effect on LBW and preterm birth
  - ○ *medium quality evidence based on strengths and limitations*
  - ○ Findings:
    - 11% of women had THC-COOH in serum or self-reported using marijuana
      - 7.8% had positive serum
      - 5.6% had positive self-report
      - 2.4% had positive serum and positive self-report
    - No significant association with marijuana use and low birth weight (OR 1.1, 95%CI 0.9-1.5)
  - ○ Strengths:
    - prospective multicenter cohort study in US
    - large multi-ethnic sample - 7470 women enrolled (43% African American, 24% Hispanic, 33% white or other)
    - interviewed women at 23-26 weeks gestation about risk factors
    - serum collected at study entry and also for a randomly selected subsample of 12% of women at 31-36 weeks gestation (3rd trimester)
      - serum tested for THC-COOH, any positive sample was confirmed by gas chromatography-mass spectrometry
    - adjusted for tobacco smoking
  - ○ Limitations:
    - study conducted 1984-1989
    - drug use categorized as yes/no variable
    - no adjustment for alcohol use as described

Small for Gestational Age (birth weight less than 10th percentile for gestational age)

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with infants being born small for gestational age.

- Day et al 1991: Maternal Health Practices and Child Development Study (Pittsburgh)
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - non significant relationship between marijuana use and small for gestational age (SGA) status.
  - Strengths:
    - longitudinal study with long term follow up (519 live born infants)
    - quantified marijuana use and assessed use in each trimester
    - study nurses were blinded to the exposure status of the infant
    - adjusted for tobacco and alcohol use
  - Limitations:
    - no statistical data included in the paper to support the finding with regards to SGA
    - Inner city, outpatient clinic population with low socioeconomic status of women, 60% completed high school, 57% of population were black - may limit generalizability of findings
- Hayatbakhsh et al 2012:
  - *medium quality of evidence based on strengths and limitations*
  - Findings:
    - 2.6% of women used cannabis during pregnancy (based on interview at 12-16 weeks of pregnancy)
    - Adjusted analysis: Significant association of cannabis use with small for gestational age (OR 2.2, 95% CI 1.8-2.7) and NICU admission (OR 2.0, 95%CI 1.7-2.4)
  - Strengths:
    - large cross-sectional study (24,874 women) at a tertiary public hospital in Australia (2000-2006)
    - adjusted for multiple variables including cigarette smoking, alcohol and other illicit drug use
  - Limitations:
    - self reported data on substance use
    - no quantification of amount of cannabis use during pregnancy
    - only looked at cannabis use at 1st prenatal visit (12-16 weeks)
    - potential inadequate confounding variables
- Saurel-Cubizolles MJ et al 2014: Cannabis use in France and preterm birth, small for gestational age
  - *low quality evidence based on strengths and limitations*
  - Findings:
    - 1.2% of women reported cannabis use during pregnancy
      - 40% reported use less than once a month, 26% reported 1-9 times per month and 15% at least 10 times per month (19% didn't answer frequency question)
    - adjusted OR for cannabis users + non-tobacco smokers showed no significant association between cannabis use less than once per month

and small for gestational age
- ○ Strengths:
  - ■ Large sample size (13,545 women), national sample
  - ■ Analyzed tobacco smokers and non-tobacco smokers separately
- ○ Limitations:
  - ■ self-report of drug use
  - ■ Interview done after delivery, could cause recall bias
  - ■ Small percentage of cannabis users in the sample (1.2%)
  - ■ limited sample size of cannabis-only users who used more than once per month - didn't allow for analysis of this group
  - ■ large confidence intervals

Decreased Birth Weight

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with decreased birth weight.
- ● Day et al 1991: Maternal Health Practices and Child Development Study (Pittsburgh)
  - ○ *low quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ No significant effect of prenatal marijuana use on birth weight, head or chest circumference.
    - ■ There was a significant effect of prenatal marijuana use in months 1 or 2 of pregnancy on infant birth length.
      - ● Smoking 1 joint per day during the 1st month of pregnancy was associated with a reduction of 1.5mm in birth length (95%CI -2.74mm to -0.28mm)
  - ○ Strengths:
    - ■ subsample of a large longitudinal study, this study included 519 live born infants of women who reported marijuana use at the rate of >2 joints per month or more during their 1st trimester and an equal number using less than that was selected randomly from the original sample
    - ■ quantified marijuana use and assessed use in each trimester
    - ■ adjusted for alcohol and tobacco use, gestational age, infant sex, race and maternal height and pregnancy weight gain
  - ○ Limitations:
    - ■ Inner city, outpatient clinic population with low socioeconomic status of women, 60% completed high school, 57% of population were black
    - ■ data not presented for findings reported
    - ■ The small changes observed may not be clinically significant
- ● El Marroun 2009 - Generation R study
  - ○ *medium quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ 214 women (2.9% of total sample) used cannabis before and during pregnancy, 41 of those women continued use throughout the pregnancy
    - ■ Adjusted analysis

- continued cannabis use during pregnancy was significantly associated with decreased fetal weight in late pregnancy (-96.44g, 95% CI -152.45g to -40.43) and decreased birth weight (-277.27g, 95% CI -409.15g to -145.39g) as compared to nonusers
- use in early pregnancy was significantly associated with decreased fetal weight in late pregnancy (-57.66g, 95% CI -86.68g to -28.65g) and birth decreased weight (-156.61g, 95% CI -224.0g to -89.23g) as compared to nonusers
- Cannabis use before pregnancy was not significantly associated with decreased fetal weight or birth weight.
- Cannabis use in early pregnancy was significantly associated with a decrease in head circumference in mid-pregnancy (-1.01mm, 95% CI -2.02mm to -0.01mm) and late pregnancy (-1.78mm, 95% CI -3.21mm to -0.34mm)
- Cannabis use before pregnancy was significantly associated with a decrease in head circumference in late pregnancy (-1.29mm, 95% CI -2.48mm to -0.09mm)
- Using infants exposed to tobacco only as a reference group, birth weight of cannabis exposed infants in early pregnancy (-95.4g; 95%CI -168.27 to -22.54) and continued exposure (-171.68g; 95%CI -308.29 to -35.07) were both significantly less. The same was true for fetal weight in late pregnancy, with decreased fetal weight in late pregnancy for fetuses exposed to cannabis in early pregnancy, -40.56g; 95%CI -71.53 to -9.60 and for fetuses continuously exposed to cannabis -67.12g; 95% CI -124.32 to -9.92) as compared to those only exposed to tobacco.
- Using cannabis in early pregnancy or throughout pregnancy resulted in significantly decreased fetal growth (11.18g/week and 14.44 g/week, respectively) as compared to non users (based on slope of the estimated growth curve).
    - Strengths:
        - large population-based cohort study in Netherlands (enrolled 2002-2006), analysis included 7,452 pregnant women)
        - adjusted for gestational age, maternal age, BMI, height education, national origin, maternal alcohol use, parity, gravidity, fetal sex and maternal psychopathology
        - utilized ultrasound assessment in early, mid and late pregnancy to estimate fetal growth
    - Limitations:
        - self report data for drug use
        - adjusted for tobacco use, but study was not able to look at effect of cannabis alone (85% of cannabis users also used tobacco)
        - small sample size of cannabis users
        - The small changes observed may not be clinically significant
- Fried et al 1987: Ottawa Prenatal Prospective Study (OPPS)

- ○ *medium quality of evidence based on strengths and limitations*
- ○ Findings:
  - ■ 15.14% of mothers used cannabis, mean amount: 6.64 +/- 19.19 joints/week (range 0.33-151.7)
  - ■ Cannabis use during pregnancy did not have a significant negative effect on any birth growth parameter (birth weight, length, head circumference)
- ○ Strengths:
  - ■ longitudinal study of 667 newborns and their mothers
  - ■ conducted maternal interviews in each trimester
  - ■ quantified cannabis use in terms of number of joints used per week
  - ■ adjusted for factors including use of tobacco, alcohol, caffeine, maternal height, weight and pregnancy weight gain, gestational length
- ○ Limitations:
  - ■ study initiated in 1978
  - ■ self report data on substance use

- ● Fergusson 2002: Avon Longitudinal Study of Pregnancy and Childhood (UK)
  - ○ *low quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ 3 categories: cannabis use at least once/week before and throughout pregnancy, once/week before or during pregnancy but not throughout pregnancy and < once/week both before and throughout pregnancy
      - ● Adjusted for covariates and gestation:
        - ○ women who used cannabis once per week before or during pregnancy but not throughout pregnancy had significantly increased effect size for both mean birth weight (89.22g, 95%CI 12.98-165.30) and birth length (0.58cm, 95%CI 0.19-0.97) as compared to nonusers
        - ○ use < once per week before and throughout pregnancy had significantly increased effect size for birth weight (58.6g, 95%CI 12.91-165.32)
  - ○ Strengths:
    - ■ large cohort study (12,129 women) in UK
    - ■ adjusted for tobacco use, alcohol and caffeine consumption, other drug use, maternal height and weight, demographic factors and gestation
  - ○ Limitations:
    - ■ cannabis use assessed by self-completion questionnaires mailed to mothers
    - ■ 70% of women who used cannabis also used tobacco, tobacco was adjusted for but unable to perform a stratified analysis of cannabis users only
    - ■ number of cannabis users was relatively small which limits statistical power
    - ■ small changes in birth parameters observed may not be clinically

significant
- English DR et al 1997: Meta-analysis of cannabis use and birth weight
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - Pooled estimates for decrease in mean birth weight associated with any cannabis use during pregnancy varied from 35g-48g.
    - "inadequate evidence that maternal cannabis use, at the levels of consumption typically reported, causes low birth weight."
  - Strengths:
    - only included studies which adjusted for cigarette smoking (10)
  - Limitations:
    - only searched Medline for articles
    - many studies do not quantify cannabis use, therefore it is difficult to combine the results
    - articles included from 1966 to November 1995 (doesn't include newer studies)
- Hingson R et al 1982: Study of effect of maternal alcohol use
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - 14% of mothers used marijuana during pregnancy (8% >1x/week)
    - Infants of mothers who used marijuana during pregnancy averaged 105 g smaller than babies of nonusers.
    - Evidence of dose response: mothers who used marijuana <3x/week had babies which were 95g smaller and mothers who used marijuana >3x/week had babies who were 139g smaller (both statistically significant)
  - Strengths:
    - large sample: 1690 mother/newborn pairs at Boston City Hospital
    - adjusted for gestational age, tobacco, alcohol or other drug use, maternal height, weight and pregnancy weight gain
  - Limitations:
    - study conducted 1977-1979
    - Study conducted to evaluate effect of alcohol
      - Of all marijuana users during pregnancy, 25% had between 1-1.99 drinks/day and 44% had >2 drinks per day (may have confounding present)
    - maternal interview done after birth, which could lead to recall bias
    - The small changes observed may not be clinically significant
- Linn et al 1983: Delivery Interview Program at Brigham and Women's Hospital
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - 1246 women reported usage of marijuana during pregnancy (~10% of total interviewed)
      - 880 women reported occasional use (7.1%), 229 reported weekly use (1.8%), 137 reported daily use (1.1%)

- ■ Adjusted analysis showed no statistically significant association with birth weight (OR 1.07, 95% CI 0.87-1.31)
  - ○ Strengths:
    - ■ adjusted for demographic characteristics, tobacco and alcohol use and maternal OB history
    - ■ large sample of women (n=12424), 1246 women with marijuana usage during pregnancy
  - ○ Limitations:
    - ■ maternal interview after birth regarding drug usage, may lead to potential recall bias (mothers who have undesirable outcome more likely to report prior use of marijuana)
    - ■ this is an early paper about the effect of prenatal marijuana use (study conducted 1977-1980)
    - ■ marijuana use characterized by use/non-use, may have limited findings
- ● Gray et al 2010: Prenatal cannabis exposure and concurrent tobacco exposure
  - ○ *low quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Cannabis exposure (by positive meconium analysis - i.e. 3rd trimester use) was associated with significantly decreased birth weight, reduced length and smaller head circumference as compared to non-exposed neonates
      - ● however most neonates were within the expected range for weight, head circumference, and length
    - ■ If exposure was expanded to include any self-report, oral fluid test or meconium result, growth parameters were no longer significantly affected by cannabis exposure
  - ○ Strengths:
    - ■ maternal interview and testing during pregnancy (oral fluid at end of each trimester and postpartum) and neonatal meconium testing (from birth, twice daily until the appearance of milk stool)
    - ■ adjusted for tobacco use
  - ○ Limitations:
    - ■ Small sample size to detect difference (86 mother/child dyads) - only 38 self-reported cannabis use during pregnancy
    - ■ excluded women with heavy cannabis consumption (>5 joints per day or >4 joints on a single occasion after pregnancy recognition)
- ● Janisse et al 2014 - gestational duration, birth weight and fetal growth
  - ○ *low quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ 24.2% of women in study used marijuana during pregnancy
    - ■ maternal marijuana use was negatively related to growth ($β$= -0.05, p <0.004)
    - ■ for marijuana, the effect on infant birth weight was due to restricted fetal growth

- ○ Strengths:
  - ■ prospective study - 3090 women followed from entry to prenatal care to delivery
  - ■ only included pregnancies with ultrasound supported estimate of gestational age
- ○ Limitations:
  - ■ Study also included alcohol, tobacco and cocaine use
  - ■ participants enrolled 1986-1998
  - ■ study limited to urban African American women at a single institution which could limit generalizability
  - ■ Women who reported at least 0.5oz of alcohol consumption per day were all invited to participate, so moderate to heavy drinkers were overrepresented in the sample
  - ■ high percentage of participants used marijuana, sample not representative of national averages
  - ■ marijuana use was categorized into 4 levels according to the % of prenatal visits in which use was reported

Birth Defects

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with neural tube defects such as anencephaly.
- ● van Gelder M et al 2009: data from National Birth Defects Prevention Study
  - ○ *Medium quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Periconceptional cannabis use not significantly associated with an increased risk of anencephaly (adjusted OR 1.7, 95%CI 0.9-3.4)
      - ● When restricting analysis to cannabis use in 1st month after conception (time of neural tube closure), adjusted OR 2.5 (95% CI 1.3-4.9), showing a significant association.
  - ○ Strengths:
    - ■ population-based, case-control study in US (1997-2003)
    - ■ 10,241 case infants with selected congenital malformations and 4967 control infants
    - ■ exposure if mother reported use of substance starting 1 month before pregnancy to the end of the 3rd month (periconceptional period)
    - ■ adjusted for maternal confounders including age at delivery, tobacco and alcohol use, race/ethnicity, education, pre-pregnancy BMI and any periconceptional folic acid use
  - ○ Limitations:
    - ■ Average postpartum telephone interview 10 months after estimated date of delivery (range 1.5-24 months), no difference between cases and controls, leading to potential recall bias
    - ■ Likely underestimate of use of illicit drugs in study (self-report, respondents often falsely deny use due to social stigma, possible

incomplete recall)
- stated that a stratified analysis was done for frequency of cannabis use however results are not reported/mentioned in the paper
- Shaw et al 1996 - Parental drug use and neural tube defects (NTD)
  - *medium quality evidence based on strengths and limitations*
  - Findings:
    - Marijuana/hash use was associated with a non-significant adjusted OR 0.74 (95%CI 0.46-1.2) for a NTD-affected pregnancy from maternal periconceptional drug use (use in period 3 months before through 3 months after conception)
    - No significantly increased NTD odds for paternal marijuana use (OR 0.86, 95%CI 0.63-1.2)
  - Strengths:
    - population-based case control study of fetuses and live born infants with neural tube defects (NTDs) between 1989-1991 in California (California Birth Defects Monitoring Program)
    - Sample: 538 face to face interviews with cases and 539 with controls, average of 4.9 months after actual or estimated date of delivery and 4.6 months for controls
    - adjusted for maternal vitamin use, race/ethnicity, education, income, age, income
  - Limitations:
    - based on self-report, potential reporting bias
    - use of prevalent (did not include spontaneous abortions) instead of incident cases
- Suarez L et al 2007 - Maternal exposures and neural tube defects
  - *low quality evidence based on strengths and limitations*
  - Findings:
    - Found no significant effect of street drug use on NTD risk when adjusted for cigarette smoking.
  - Strengths:
    - population-based case-control study, Mexican-American women in Texas
    - compared NTD-affected pregnancy (1995-2000) to controls in the same area
    - adjusted for tobacco use
  - Limitations:
    - 175 cases and 221 controls
    - small number of marijuana users (2% of women in study reported marijuana use)
    - did not look at marijuana separately (street drug use included cocaine and marijuana)

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with gastroschisis.

- Forrester MB 2006 - Gastroschisis and prenatal drug use
    - *low quality evidence based on strengths and limitations*
    - Findings:
        - prenatal marijuana use rate was significantly higher among gastroschisis cases than among the total population (275.23 per 10,000 live births for gastroschisis cases and 26.19 per 10,000 live births for total cases)
        - pattern of prenatal marijuana use showed the highest rates in the youngest age group and decreased with increasing maternal age (similar to the gastroschisis rates)
    - Strengths:
        - use of Hawaii birth defects registry, infants and fetuses delivered during 1986-2002 (total of 316,508 live births, 109 total gastroschisis cases)
        - prenatal drug use based on positive toxicology screen of mother or infant during or shortly after delivery or report of drug use in the medical record
    - Limitations:
        - small sample size to form conclusions (3 gastroschisis cases with marijuana use out of 109 total gastroschisis cases)
        - limited information on when drug use occurred during pregnancy
        - toxicology screening was done around delivery and gastroschisis likely occurs within the first several months of pregnancy, so cannot know if the mother was using at that time, also used self-report data
        - didn't adjust for other potential risk factors
- van Gelder M et al 2009: data from National Birth Defects Prevention Study
    - *Medium quality of evidence based on strengths and limitations*
    - Findings:
        - increased crude OR for having a child with gastroschisis with periconceptional use of cannabis, but maternal age was a strong confounder and adjusted OR showed no statistically significant association (OR 1.3, 95% CI 0.9-1.8)
    - Strengths:
        - population-based, case-control study in US (1997-2003)
        - 10,241 case infants with selected congenital malformations and 4967 control infants
        - exposure if mother reported use of substance starting 1 month before pregnancy to the end of the 3rd month (periconceptional period)
    - Limitations:
        - Average postpartum telephone interview 10 months after estimated date of delivery (range 1.5-24 months), no difference between cases and controls, potential recall bias
        - Likely underestimate of use of illicit drugs in study (self-report, often falsely deny use due to social stigma, possible incomplete recall)

■ stated that a stratified analysis was done for frequency of cannabis use however results are not reported/mentioned in the paper

We found <u>limited</u> evidence that maternal use of marijuana during pregnancy is associated with isolated, simple ventricular septal defects (heart defects).

- Williams et al 2004: Maternal lifestyle factors and Risk for Ventricular Septal Defects (VSD)
    - *medium quality evidence based on strengths and limitations*
    - Findings:
        - Maternal cannabis use was associated with a crude OR of 2.35 (95%CI 1.43-3.86) of isolated, simple VSD when utilizing maternal self-report and crude OR of 2.21 (95%CI 1.11-4.38) when utilizing paternal proxy report
            - Frequency of use analysis: ≤2 days per week, crude OR 2.20 (95%CI 1.22-3.93) and ≥3 days per week, crude OR 3.73 (95%CI 1.56-8.96) for maternal self-report data, not statistically significant when utilizing paternal proxy report data
        - Adjusted OR for maternal cannabis use (adjusted for maternal age, race, overt diabetes and multivitamin use) 1.90 (95%CI 1.29-2.81) [comparing no use, light use (≤2 days per week) and heavy use (≥3 days per week)]
    - Strengths:
        - population-based case-control study
        - 122 infants with isolated simple VSD for this analysis(out of larger study of 4929 case infants with birth defects), 3029 control infants
        - Metropolitan Atlanta Congenital Defects Program utilized active case-finding procedures which have previously been shown to be highly sensitive
        - use of maternal and paternal questionnaires, self-report and proxy report
        - Data analyzed for women who reported marijuana use with other drugs and separately for women who only reported marijuana use (and results did not change)
    - Limitations:
        - Only included infants who had a defect noted in the first year of life
        - self-report/proxy report data only, no biological samples collected
        - cases identified in infants born between 1968-1980)

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with birth defects.

- Linn et al 1983: Delivery Interview Program at Brigham and Women's Hospital
    - *low quality evidence based on strengths and limitations*
    - Findings:
        - Adjusted analysis showed a non-significant OR of 1.36, 95% CI 0.97-1.91 for major malformations in marijuana users vs. non-users
    - Strengths:
        - large sample (12424 women, 1246 of those who reported use of

marijuana)
- ■ adjusted for demographic characteristics, tobacco and alcohol use and maternal OB history
  - ○ Limitations:
    - ■ major malformations included were those that were diagnosed during the delivery hospitalization (many present at a later time)
    - ■ potential recall bias (mothers who have undesirable outcome more likely to report prior use of marijuana)
    - ■ this is an early paper about the effect of prenatal marijuana use (study conducted 1977-1980)
- ● Day et al 1991: Maternal Health Practices and Child Development Study (Pittsburgh)
  - ○ *low quality of evidence based on strengths and limitations.*
  - ○ Findings:
    - ■ no significant association between marijuana use in any trimester or any of the first 3 months and minor physical anomalies.
    - ■ Number of major physical anomalies seen in the study was insufficient for analysis.
  - ○ Strengths:
    - ■ longitudinal study with large sample size (519 live born infants)
    - ■ quantified marijuana use and assessed use in each trimester
    - ■ adjusted for tobacco and alcohol use
  - ○ Limitations:
    - ■ based on examinations of the infant between 24 and 48 hours of life (many anomalies present later)
    - ■ Inner city, outpatient clinic population with low socioeconomic status of women, 60% completed high school, 57% of population were black
- ● Forrester MB and Merz RD 2007: Birth defects and prenatal drug use in Hawaii
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Prenatal marijuana rates were significantly higher than expected for 21 (39%) of the 54 types of birth defects
      - ● mainly CNS defects, cardiovascular system defects, oral clefts, GI system and limbs
    - ■ If other drug use was excluded, than rates of prenatal marijuana use were significantly higher than expected for 19 (35%) of the 54 types of birth defects
  - ○ Strengths:
    - ■ use of statewide, populations-based registry for adverse pregnancy outcomes (total live births 316,508, total cases with one of 54 birth defects was 7293 infants or fetuses and 829 cases of prenatal marijuana use among deliveries 1986-2002)
    - ■ cases included all infants and fetuses delivered 1986-2002 with a report of drug use (meth, cocaine or marijuana) or a diagnosis of 54 selected birth defects

- - ■ Drug use based on mention of illicit drug use in medical record or positive toxicology screen for the mother or infant during or shortly after delivery
    - ○ Limitations:
      - ■ small number of cases for many birth defects categories which limited the ability to identify statistically significant differences and resulting in large confidence intervals
      - ■ no adjustment for confounding factors (ex: demographics, health behaviors or prenatal care)
      - ■ use of illicit drugs at any time during pregnancy
      - ■ no dose or frequency information on drug use

HEALTH EFFECTS OF PRENATAL USE ON EXPOSED OFFSPRING

SIDS

Based on <u>limited</u> evidence, there does not appear to be an association between maternal use of cannabis during and after pregnancy and SIDS.
- ● Scragg RKR et al - Maternal cannabis use and SIDS
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Maternal use of cannabis in pregnancy
      - ● adjusted for main confounders, OR 1.3 (95%CI 0.69-1.87)
      - ● multivariate OR 1.18 (95%CI 0.76-1.85)
    - ■ attributable risk of SIDS from cannabis exposure (from univariate analysis) was 14% (lower than tobacco - 51%)
  - ○ Strengths:
    - ■ reviewed obstetric records and completed in home interviews with parents
    - ■ adjusted for main confounders: ethnicity, maternal tobacco, SES, mother's marital status, age at first pregnancy, infant's age
    - ■ multivariate analysis controlled for region, time of day, season, age mother left school, mother's age, parity, attendance at antenatal clinic and educational classes, infant's sex, birth weight, gestation, sleep position, breastfeeding and bed sharing
  - ○ Limitations:
    - ■ New Zealand case-control study (485 cases, 1800 controls), births October 1, 1987-September 30, 1990
    - ■ possible underreporting of cannabis use (social desirability bias, marijuana is illegal in New Zealand)
    - ■ missing data from uninterviewed parents (81% of parents of cases interviewed and 88.4% of controls interviewed), ethnic differences in non-respondents (more likely to be Maori)
- ● Klonoff-Cohen H et al 2001: Maternal/Paternal Drug use and SIDS
  - ○ *low quality evidence based on strengths and limitations*

- ○ Findings:
  - ■ SIDS outcome was not significantly associated with maternal cannabis use during conception (OR 1.1, 95% CI 0.6-2.0) or pregnancy (OR 0.6, 95%CI 0.3-1.6)
    - ● maternal smoking during pregnancy was a confounder
- ○ Strengths:
  - ■ case-control study of 239 infants who died with a diagnosis of SIDS in southern CA between 1989-1992 matched with 239 healthy infants by birth hospital, date of birth, age and sex
  - ■ adjusted for maternal socioeconomic status, alcohol use during pregnancy, sleep position, bed sharing, infant risk factors
- ○ Limitations:
  - ■ small number of mothers who reported drug use during conception or pregnancy, low power to detect statistically significant associations
  - ■ 100 eligible cases were unable to be located
  - ■ self-report drug histories
  - ■ telephone interviews 6-12 months after infant's death (common protocol), possible recall bias
  - ■ large confidence intervals for adjusted OR

We found <u>mixed</u> evidence for whether or not maternal use of marijuana during pregnancy is associated with newborn behavior issues.
- ● de Moraes Barros et al 2006:
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Compared exposed to non-exposed infants, exposed infants were more irritable, less responsive to calming maneuvers by the examiner, cried more during exam and exhibited more jitteriness and startles. Exposed infants had higher arousal scores after adjusting for sex, gestational age and postnatal age and a higher excitability score after adjusting for gestational age.
  - ○ Strengths:
    - ■ cross-sectional study
    - ■ Infants had Neonatal ICU Network Neurobehavioral Scale (NNNS) neurobehavioral assessment between 24 and 72 hours of life.
  - ○ Limitations:
    - ■ small sample size: 26 full term neonates born to adolescent mothers (July 2001-November 2002) who had used marijuana (4.6% of adolescent mothers) at one city hospital in Brazil.
    - ■ no quantification of marijuana use (just positive hair testing which shows use in last 3-5 months)
- ● Dreher 1994: Study of prenatal marijuana exposure in rural Jamaica
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:

- ■ No significant difference at day 3 in performance between exposed and non-exposed infants
          - ■ At 1 month, exposed infants had significantly higher scores on the Autonomic and Reflex clusters as well as the General Irritability item (they were less irritable) as compared to non-exposed infants
            - ● On further analysis, maternal education was significantly correlated with this finding of higher autonomic scores.
      - ○ Strengths:
        - ■ use of Brazelton Neonatal Behavioral Assessment Scale
      - ○ Limitations:
        - ■ Small sample size (24 exposed and 20 non-exposed infants)
        - ■ no adjusted analysis performed
        - ■ In the area of rural Jamaica this study was conducted in, heavy use of marijuana by women is associated with a higher education level and greater financial independence (capacity to create a supportive postnatal environment)
        - ■ short term follow up of infants (1 month)
- ● Richardson GA et al 1989:
  - ○ *medium quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ prenatal marijuana use was not a significant predictor of Neonatal Behavioral Assessment Scale (NBAS) performance on day 2 of life
    - ■ infants of women who continued to use a substance (alcohol, tobacco or marijuana) did not show differential NBAS performance from infants whose mothers never used or stopped using the substance
  - ○ Strengths:
    - ■ longitudinal prospective study (373 infants)
    - ■ NBAS examiners were blinded of infants' exposure status
    - ■ interviews done at fixed time points during pregnancy
    - ■ multivariate analysis adjusted for alcohol, tobacco and marijuana use as well as demographic and socioeconomic factors
  - ○ Limitations:
    - ■ Sample with low socioeconomic status, average educational level of 11.8 years, 51% white and 49% black
    - ■ NBAS examiner was the strongest predictor of neonatal behavior in this study. 5 examiners were used in this study, 4 separate regression analyses were performed, each eliminating one of the examiners and results were unchanged
- ● Lester and Dreher 1989: Marijuana use in Pregnancy and newborn cry (Jamaica)
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Infants of women who used marijuana during pregnancy had higher-pitched and more variable cry

- could suggest respiratory involvement or an effect of marijuana on the central nervous system
      - ■ Frequency of marijuana smoking was inversely correlated with the median first formant (F1) of the cry
    - ○ Strengths:
      - ■ at the time of the study (late 1980's), marijuana in Jamaica had higher concentration of THC than that seen in the US
      - ■ marijuana use determined for each trimester
      - ■ rare use of tobacco, alcohol or other drugs by pregnant women in this sample
    - ○ Limitations:
      - ■ small sample size (20 exposed and 20 non-exposed infants)
      - ■ study conducted in Jamaica in the late 1980's which limits generalizability
      - ■ users smoked marijuana cigars or drank marijuana tea
      - ■ marijuana use based on self-report or direct observation

We found <u>moderate</u> evidence that maternal use of marijuana during pregnancy is associated with decreased growth in exposed offspring.
- ● Cornelius et al 2002: cohort of adolescent mothers and their offspring (part of MHPCD project, Pittsburgh)
    - ○ *medium quality evidence based on strengths and limitations*
    - ○ Findings:
      - ■ 39% reported use of marijuana in year before pregnancy, 15% in 1st trimester, 4% in 2nd trimester, 3.5% in 3rd trimester
      - ■ At age 6, 2nd trimester use predicted lower height (-1.13 inches, p<0.01)
      - ■ No significant effect of prenatal exposure to alcohol, tobacco or marijuana on BMI, ponderal index or weight for height z scores
    - ○ Strengths:
      - ■ longitudinal study of adolescent mothers and their offspring
      - ■ 345 offspring evaluated at 6 years, out of original 413 eligible from prenatal phase
      - ■ adjusted for tobacco, alcohol use (prenatal and current use), maternal factors (demographic, psychosocial, height), current home environment
    - ○ Limitations:
      - ■ 69% African-American, 31% Caucasian, low SES, 78% completed HS which may limit generalizability
      - ■ recruitment, prenatal and delivery phases 1990-1994
      - ■ 2nd and 3rd trimester use was characterized as use/nonuse due to low numbers of users in these trimesters
- ● Fried et al 1999: Ottawa Prenatal Prospective Study 12 year follow up
    - ○ *low quality evidence based on strengths and limitations*
    - ○ Findings:
      - ■ 3 groups of prenatal usage: no use, mild/moderate use (up to 6 joints/week), heavy use (at least 6 joints per week)

- Average scores for head circumference at each age were smallest for the heavy marijuana group, intermediate for moderate group and largest for non-users (statistically significant in 9-12 year olds, remained significant after adjusting for cigarette and alcohol use)
- First year weight gain was positively related to maternal marijuana prenatal use, children of heavy users gained more weight than other groups.
- Female children in heavy marijuana group were significantly lighter than male children at 12 months old (significant after adjustment for tobacco and alcohol use)
  - Strengths:
    - adjusted for maternal demographic, social and height/weight factors, paternal weight and height as well as method and length of time of breast feeding (also tobacco and alcohol use)
  - Limitations:
    - small sample size (follow up cohort of 140 children of women who reported any use of marijuana, alcohol >0.85oz average daily or smoked an average of 16 mg nicotine per day +50 children of women with no substance use)
    - actual measurements of groups at each age not listed, calculated standardized z scores
    - assessed exposure of child to secondhand tobacco smoke postnatally, however paper does not state that exposure to marijuana postnatally warecorded or considered

We found <u>moderate</u> evidence that maternal use of marijuana during pregnancy is associated with decreased IQ scores in exposed offspring.
- Day et al 1994: relationship between prenatal marijuana exposure and performance on Stanford-Binet Intelligence Scale at age 3
  - *medium quality of evidence based on strengths and limitations*
  - Findings:
    - For total cohort: no significant effects of marijuana use during any trimester on composite score of Stanford-Binet.
    - For offspring of African-American women: 1st trimester marijuana use significantly predicted a decrease of 1.3 IQ points per joint smoked per day on the verbal reasoning subscale, 2nd trimester use was a significant predictor of performance on the short term memory subscale (decrease of 1.6 points per joint per day).
    - For offspring of white women: no significant effect of prenatal marijuana use in any trimester.
    - Preschool/day care attendance was a significant predictor of better performance on the Stanford-Binet Scale.
      - For total cohort: (considering interaction)
        - interaction of 1st trimester marijuana use by

> preschool/daycare attendance was significant and positive for composite and verbal reasoning subscale
>> ○ effect on of 2nd trimester use was a significant 2.3 point decrease per joint per day (not significant with interaction term)
>> ● For African-American offspring:
>>> ○ 1st trimester use had 0.9 points/joint/day decrease on composite score, 1.1 points/joint/day decrease on short-term memory subscale and 1.5 points/joint/day decrease on verbal reasoning subscale.
>>> ○ 2nd trimester use had decrease of 1.8 points/joint/day for short term memory. Interaction between marijuana use and preschool/daycare attendance not significant in this group
>> ● For white offspring:
>>> ○ For composite score, 2nd trimester effect showed a decrease of 8.9 points/joint/day if a child did not attend preschool/daycare and was offset by an increase in IQ score among children who did attend preschool/daycare.
>>> ○ Also was a significant main effect of 2nd trimester use on abstract/visual reasoning subscale (decrease of 7.6 points/joint/day) after controlling for the effect of the interaction.
> ■ Authors summarize: for both white and African-American offspring, prenatal marijuana use was associated with significantly decreased scores on the Stanford-Binet, but the decrease was offset by preschool/daycare attendance only in white children.
- ○ Strengths:
  - ■ high retention rate of MHPCD study (analyzed 655 of original 763 infants)
  - ■ categorization of marijuana use into average daily joints (ADJ)
  - ■ assessment of drug use at each trimester and each follow up point
  - ■ comprehensive assessment of current factors that influence cognitive development (home environment, maternal cognitive ability, social and demographic factors) and adjusted for those factors
- ○ Limitations:
  - ■ Initial recruitment for study was 1983-1985
  - ■ mothers were generally low income with a high school education and sample was 48% white, 52% black (could limit generalizability)
- ● Goldschmidt L et al 2008 - Prenatal MJ and Intelligence at Age 6 (MHPCD)
  - ○ *medium quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ 2nd trimester heavy marijuana exposure (>1 joint cigarette per day) was significantly associated with the child's Stanford-Binet Intelligence Scale (SBIS) composite score after controlling for other predictors (5 point

deficit in composite score as compared to non-exposed)
- 1st trimester heavy marijuana exposure significantly related to verbal reasoning (deficit of 2.6 points as compared to non-exposed)
- Heavy marijuana exposure in 2nd (deficit of 8 points)and 3rd (deficit of 5 points) trimester significantly predicted performance on the quantitative reasoning subscale after controlling for other predictors
- 2nd trimester heavy exposure was significantly associated with a decreased score on short-term memory subscale (-4.5 points)
- ○ Strengths:
  - high retention rate of MHPCD study (648 children in this analysis)
  - categorization of marijuana use into average daily joints (ADJ)
  - assessment of drug use at each trimester and each follow up point
  - comprehensive assessment of factors that influence cognitive development (home environment, maternal cognitive ability, social and demographic factors)
- ○ Limitations:
  - participants tended to be low income, most only had high school education and were 47% white, 53% African-American - may limit generalizability
  - use of SBIS - does not measure specific aspects of cognition such as learning, memory, problem solving and concept formation

We found <u>moderate </u>evidence that maternal use of marijuana during pregnancy is associated with reduced cognitive function in exposed offspring.
- Willford et al 2010: MHPCD f/u age 16-18
  - ○ *medium quality evidence based on strengths and limitations*
  - ○ Findings:
    - prenatal marijuana use was significantly associated with decrease in processing speed and interhemispheric coordination
  - ○ Strengths:
    - long term follow up cohort, 320 mother/child dyads for this analysis
    - prenatal marijuana use measured during each month of the 1st trimester and in 2nd and 3rd trimester
    - average daily joints calculated for each trimester
    - adjusted for home environment, prenatal exposure to alcohol or tobacco and age, life events, maternal depression, anxiety and hostility, also maternal intellectual ability (measured at 10 year f/u)
    - also considered adolescent drug use, depression and anxiety
  - ○ Limitations:
    - low socioeconomic status of sample
    - sample contained less than half of the original sample due to inability to get 269 of the subjects to complete the bimanual coordination task (BCT) for various reasons

- Fried et al 2003 - Cognitive functioning in 13-16 year olds (OPPS f/u)
    - *low quality of evidence based on strengths and limitations*
    - Findings
        - Compared children of heavy users (≥6 joints/week) vs. none/light users (<6 joints/week)
            - After adjustment, there was a significant association found with children of heavy users having slower response times on the Abstract Designs latency section (visual memory task) than none/light users (p≤0.05)
            - After adjustment, there was a significant negative association with performance on the Peabody Spelling assessment (p≤0.05)
    - Strengths
        - 157 children tested out of long term follow up cohort (190 children)
        - multiple tests used to assess multiple aspects of cognition
        - adjusted test scores for age of subject
        - adjusted for prenatal exposure, SES, maternal age, maternal drug use (tobacco, alcohol, other drugs), postnatal variables (SES, current maternal tobacco and marijuana use, home environment)
    - Limitations
        - small sample sizes for marijuana analysis (n=25 for heavy users)
        - achievement tests are more highly dependent on formal learning experiences in school or home
        - study started in 1978
        - children of non-users and light users included in the same comparison group
- Smith AM et al 2004 - Effects of prenatal use on response inhibition - an fMRI study
    - *low quality of evidence based on strengths and limitations*
    - Findings:
        - there was a significant positive relationship between bilateral prefrontal cortex activity (mediates inhibitory functions) and the amount of prenatal marijuana exposure
        - there was an attenuation of activity in the left cerebellum with increase prenatal exposure to marijuana during response inhibition
        - After adjustment, prenatally exposed participants had significantly more errors of commission than the non-exposed group

    - Strengths:
        - controlled for current drug use (urine testing prior to imaging and completion of a drug questionnaire), participant excluded if positive for cocaine, opiates or amphetamine), also adjusted for current marijuana, nicotine, alcohol and IQ
        - adjusted for prenatal exposure to nicotine, alcohol and caffeine
    - Limitations:

- small sample size - 35 participants from the OPPS f/u sample (16 exposed to prenatal marijuana, 15 not exposed)
- sample is predominantly white, middle class which could limit generalizability
- 13 of the 31 participants tested positive for cannabis, however there were no significant differences between the prenatally exposed and the non-prenatally exposed groups in the amount of cannabinoids in their urine and current use of marijuana was adjusted for

We found <u>moderate</u> evidence that maternal marijuana use during pregnancy is associated with decreased academic ability of exposed offspring.
- Fried et al 1997: Ottawa Prenatal Prospective Study f/u
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - Prenatal marijuana exposure was not significantly related to either the reading or language outcomes at age 9-12
  - Strengths:
    - multiple tests to assess reading and language/auditory domains were administered to the children as well as 2 brief questionnaires to examine depression and anxiety levels
    - adjusted for maternal demographic factors and educational level as well as postnatal variables such as current maternal marijuana use, socio-demographic characteristics
  - Limitations
    - small sample size (long term follow up cohort of 131 children of women who reported any use of marijuana, alcohol >0.85oz average daily or smoked an average of 16 mg nicotine per day +50 children of women with no substance use)
    - separated users into 3 groups (≤1 joint per week, >1 and <6 joints per week and ≥6 joints per week) and cell sizes were small for the more frequent use groups (n=11 and n=20, respectively)
- Goldschmidt L et al 2004 - Prenatal exposure and academic achievement at age10 (MHPCD study f/u)
  - *medium quality evidence based on strengths and limitations*
  - Findings:
    - After adjustment, 1st trimester heavy use significantly predicted deficits in the WRAT-R reading and spelling scores and a lower rating on the teacher's evaluations
      - 1st trimester heavy use also significantly associated with the child's self-reported depression and anxiety symptoms.
      - When these scores were included in the regression analysis, 1st trimester heavy use was no longer a significant predictor of academic performance as measured in this study
    - After adjustment, 2nd trimester use was a significant predictor of reading

comprehension scores (PIAT-R) and 2nd trimester heavy use was significantly associated with a lower rating teachers' evaluation.
- 2nd trimester exposure was not significantly related to depression or anxiety symptoms
■ 2nd trimester marijuana use also significantly predicted underachievement, after adjustment OR 2.0 (95% CI 1.05-3.8, p=0.04) as compared to non-users
○ Strengths:
■ high retention rate of MHPCD study (606 children evaluated)
■ categorization of marijuana use into average daily joints (ADJ)
■ assessment of maternal drug use at each trimester and each follow up point
■ utilized the Wide Range Achievement Test - Revised (WRAT-R), reading comprehension subtest of the Peabody Individual Achievement Test - Revised (PIAT-R) and teacher's report of child's performance
■ also assessed child's depression and anxiety symptoms
■ adjusted for maternal prenatal tobacco use, maternal current substance use, socio-demographic factors, child characteristics and environment,
○ Limitations:
■ for regression analysis, marijuana use dichotomized to heavy use (≥1 joint per day) and no use + non-heavy use (<1 joint per day)
■ women were not heavy users of marijuana
■ variables such as motivation, social skills and parent involvement in child's education (all predictors of school achievement) were not included in the analysis
■ sample was predominantly low socioeconomic status
● Goldschmidt et al 2012: School achievement in 14 year olds (MHPCD f/u)
○ *medium quality evidence based on strengths and limitations*
○ Findings:
■ after adjustment, 1st trimester maternal marijuana use (>1 joint per day) was significantly associated with lower Weschsler Individual Achievement Test (WIAT) Screener (basic reading, math reasoning and spelling) composite score (-2.9 points, p<0.05)
■ 1st trimester use (>1 joint per day) significantly associated with a deficit in the basic reading subscale (-3.3 points, p<0.05)
○ Strengths:
■ long term follow up cohort, 524 mother/child dyads for this analysis
■ marijuana use measured during each month of the 1st trimester and in 2nd and 3rd trimester
■ average daily joints calculated for each trimester
■ adjusted for current maternal substance use, home environment, prenatal exposure to alcohol or tobacco and age
■ also considered IQ, depression symptoms, inattention and effects of early initiation of marijuana use (results from previous studies)

- ○ Limitations:
  - ■ low socioeconomic status of the sample

We found <u>moderate</u> evidence that maternal use of marijuana during pregnancy is associated with attention problems in exposed offspring.
- ● El Marroun 2011: Generation R study (Rotterdam, Netherlands) - 18 month f/u
  - ○ *low quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ Prenatal exposure to cannabis was associated with increased scores on the aggressive behavior scale and the attention problem scale in girls only at 18 months old (using Child Behavior Checklist for toddlers CBCL 1 ½-5yrs).
    - ■ In a logistic regression analyses using the cut-off score of the CBCL, the only significant result was that girls had an increased odds for developing attention problems (OR 2.75, 95% CI: 1.27-5.96, p=0.01)
  - ○ Strengths:
    - ■ large general population birth cohort (4077 for 18 month f/u out of 5512 initial study population)
  - ○ Limitations:
    - ■ even with a large cohort, only 88 women used cannabis in pregnancy, therefore there was a small sample size for analysis (especially with stratifying by gender)
    - ■ ethnic differences in sample may limit generalizability to US population (i.e. women using cannabis during pregnancy were more often of Surinamese and Antillean national origin and women that continued use throughout pregnancy were more likely to be Turkish and less likely to be Moroccan)

- ● Noland JS et al 2005 - Prenatal drug use and selective attention in preschoolers
  - ○ *low quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ there was a non-significant positive correlation between the average severity of marijuana exposure and the rate of omission errors on the picture deletion task (PDT)
    - ■ severity of first trimester marijuana use was identified as the best marijuana exposure predictor of PDT omission error rate (p=0.03)
    - ■ When adjusting for severity of current caregivers use of marijuana, 1st trimester marijuana severity of use was not longer statistically significant
  - ○ Strengths:
    - ■ longitudinal prospective study (Case Western Reserve University), n=330 children (long term follow up for prenatal exposure to cocaine)
    - ■ child testers blinded to substance exposure of children
    - ■ prenatal exposure assessed via biological samples taken during the birth hospital stay and a post partum interview (2 weeks post partum)

- ○ Limitations:
  - ■ high percentage of marijuana users also used other substances (tobacco, alcohol or cocaine) - participants in a longitudinal study evaluating effects of prenatal cocaine exposures
  - ■ use of severity score for marijuana - frequency estimate (days/week) multiplied by the daily amount of joints for each of 4 time periods which were averaged into a single average severity score
- ● Goldschmidt L et al 2000 - Prenatal exposure and behavior problems at age 10
  - ○ *medium quality of evidence based on strengths and limitations*
  - ○ Findings:
    - ■ After adjustment, 1st trimester marijuana use remained a significant predictor of the attention scale of the SNAP (p<0.01)
    - ■ After adjustment, 3rd trimester marijuana use was significantly associated with higher scores on the hyperactivity (p<0.001), attention (p<0.01) and impulsivity (p<0.01) scales of the SNAP
    - ■ 1st trimester heavy use associated with significantly higher scores on the delinquency scale of the CBCL.
      - ● inattention symptoms mediated the effect of prenatal marijuana exposure on delinquency
    - ■ No significant associations between prenatal marijuana use and the TRF scales
  - ○ Strengths:
    - ■ high retention rate of MHPCD study (635 children evaluated)
    - ■ assessment of maternal drug use at each trimester and each follow up point
    - ■ categorization of marijuana use into average daily joints (ADJ)
    - ■ assessed child behavior problems with Swanson Noland and Pelham assessment (SNAP, elicits symptoms for DSM-III ADD with hyperactivity) and Child Behavior Checklist (CBCL) -both completed by mother/caregiver and Teacher's Report Form (TRF) - completed by teacher
    - ■ adjusted for SES, maternal psychosocial characteristics, child's home environment, current maternal substance use, prenatal substance use
  - ○ Limitations:
    - ■ Only 575 children had teacher's reports
    - ■ sample was predominantly low socioeconomic status
- ● Fried et al 2001: OPPS f/u 13-16 yrs
  - ○ *medium quality evidence based on strengths and limitations*
  - ○ Findings:
    - ■ maternal marijuana use was significantly associated with poorer performance on the stability factor (one of the 5 factors of the model of attention)

- - - Heavy maternal marijuana use (≥6 joints per week) was associated with factor scores reflecting less consistent reaction time over blocks and more omissions
      - Maternal marijuana use was not significantly associated with the other 4 factors (shift/flexibility, encode/retain, impulsivity, focus/execute)
  - Strengths:
    - long term follow up of longitudinal study (152 of original 190 children)
    - adjusted for prenatal and current: parental education, family income, maternal drug use, secondhand smoke exposure (maternal and child), family status, adolescent's current smoking habits
    - subjects completed 11 tests that consisted of tasks to assess the 5 models of attention
  - Limitations:
    - no measures of attentional deficits for the mother or father were available
    - study initiated in 1978

We found <u>limited</u> evidence that maternal use of marijuana during pregnancy is associated with increased depression symptoms in exposed offspring.

- Gray KA et al. 2005 - Prenatal exposure and effect on child depressive symptoms at age 10 (MHPCD f/u study)
  - *medium quality of evidence based on strengths and limitations*
  - Findings:
    - prenatal marijuana exposure in 1st and 3rd trimesters significantly predicted more symptoms of depression in children after controlling for significant prenatal predictors and current correlates of child depression
  - Strengths:
    - high retention rate of MHPCD study (prospective study with long term follow up) n=636
    - categorization of marijuana use into average daily joints (ADJ)
    - assessment of drug use at each trimester and each follow up point
    - mother and child interviewed separately in a non-clinical environment
    - staff interviewers were unaware of mother's prenatal and current substance use history
    - conducted 3 regression analyses, one controlling for significant prenatal covariates, one controlling for the 10 year significant covariates and a 3rd with significant variables from the 1st and 2nd analyses
  - Limitations:
    - study looked at depression symptoms, not depression diagnosis
    - possible limited generalizability of study - sample was predominantly low socioeconomic status

We found <u>insufficient</u> evidence to suggest that maternal marijuana use during pregnancy is associated with psychosis symptoms in exposed adolescent offspring.

- Zammit S et al 2009 - Avon Longitudinal Study f/u (UK)

- - *low quality of evidence based on strengths and limitations*
  - Findings:
    - after adjustment, maternal cannabis use during pregnancy was not significantly associated with psychosis-like symptoms (adjusted OR 0.94, 95% CI 0.62-1.41, p=0.755) based on the PLIKSi (psychosis like symptoms semi-structured interview)
  - Strengths:
    - 12 year follow up of large longitudinal study
  - Limitations:
    - poor retention at 12 year time point - sample consisted of 6356 children from original cohort of 14,062
    - did not assess current maternal substance use (only assessed maternal substance use up to 47 months after birth)
    - children who did not complete the assessment were more likely to have mothers who smoked tobacco and used cannabis as compared to those who did complete it

We found <u>limited</u> evidence that maternal marijuana use during pregnancy is associated with delinquent behaviors in exposed offspring.
- Day et al 2011: Prenatal exposure and delinquent behaviors
  - *medium quality evidence based on strengths and limitations*
  - Findings:
    - After adjustment, offspring of heavier marijuana users (>1 joint per day) were significantly more likely to report delinquent behavior at age 14 (OR 1.76, 95%CI 1.05-2.96) as compared to non-users or those who used lower amounts
    - Association between prenatal marijuana exposure and delinquent behavior was mediated by depressive symptoms and attention problems at age 10
  - Strengths:
    - long term follow up cohort, 525 mother/child dyads for this analysis
    - marijuana use measured during each month of the 1st trimester and in 2nd and 3rd trimester
    - average daily joints calculated for each trimester
    - adjusted for current maternal substance use, home environment, prenatal exposure to alcohol or tobacco and age
    - also considered IQ, depression symptoms, inattention (results from previous studies)
    - utilized maternal report (Child Behavior Checklist) and adolescent self-report (Self-Report Delinquency Scale)
  - Limitations
    - low socioeconomic status of the sample

- there are multiple pathways to delinquency and the effects of prenatal marijuana exposure only explain a portion of the delinquency in the adolescent population

We found <u>mixed</u> evidence for whether or not maternal marijuana use during pregnancy is associated with frequency of marijuana use by the exposed offspring during adolescence.
- Day et al 2006: Prenatal marijuana use and marijuana use by offspring at age 14
  - *medium quality of evidence based on strengths and limitations*
  - Findings:
    - When adjusted for significant current child behavioral characteristics:
      - prenatal marijuana exposure was not significantly associated with age of onset of offspring marijuana use
      - prenatal marijuana exposure was significantly associated with frequency of offspring marijuana use (OR 1.3 for adolescents who were exposed to 1 joint/day as compared to those with no exposure)
  - Strengths:
    - 580 of original 763 offspring evaluated at 14 years
    - participants evaluated at time point with a standardized protocol (maternal psychological, social and environmental factors, demographics, substance use, child's cognitive, behavioral, psychological and physical development)
    - adjusted for prenatal substance use, maternal and child factors
  - Limitations
    - low socioeconomic status of participants
    - original cohort was weighted to substance-using women, therefore results may be less generalizable
- Porath AJ and Fried PA 2005 - Prenatal marijuana use and later drug use in offspring (OPPS follow up)
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - no significant association between prenatal exposure to marijuana and offspring's regular use of marijuana
    - no significant association between prenatal marijuana exposure and gender of offspring and initiation or regular use of marijuana
  - Strengths:
    - longitudinal study with long term follow up (152 adolescents), 16-21 years old)
    - use was determined via self-report and verified with a urine test
  - Limitations:
    - relatively small sample size (especially for gender-specific analyses) - 190 children selected from original cohort for follow up studies
    - sample predominantly white, middle class

- Study started in 1978
- no data collected on parent's current use of substances
- use of marijuana in pregnancy categorized into use and no use

We found <u>insufficient</u> evidence that maternal marijuana use during pregnancy is associated with initiation of marijuana use by exposed offspring during adolescence.
- Porath AJ and Fried PA 2005 - Prenatal marijuana use and later drug use in offspring (OPPS follow up)
  - *low quality of evidence based on strengths and limitations*
  - Findings:
    - Significant association between prenatal exposure to marijuana and offspring's initiation of marijuana use (OR 2.76, 95%CI 1.11-6.86)
    - no significant association between prenatal marijuana exposure and gender of offspring and initiation or regular use of marijuana
  - Strengths:
    - longitudinal study with long term follow up (152 adolescents), 16-21 years old)
    - use was determined via self-report and verified with a urine test
  - Limitations:
    - relatively small sample size (especially for gender-specific analyses) - 190 children selected from original cohort for follow up studies
    - sample predominantly white, middle class
    - Study started in 1978
    - no data collected on parent's current use of substances
    - use of marijuana in pregnancy categorized into use and no use
    - large confidence interval (95%CI 1.11-6.86)

MARIJUANA USE AND BREASTFEEDING

Epidemiology of marijuana use and breastfeeding:
- There is limited epidemiologic information about marijuana use in breastfeeding women, as distinct from data in pregnant women.

Biological evidence shows that THC is present in the breast milk of women who use marijuana.
Biological evidence shows that infants who drink breast milk containing THC absorb and metabolize the THC.
  - Two women who used marijuana while breastfeeding had THC in their breast milk. One of them had plasma tested as well, with 8x higher concentration in the breast milk compared with plasma. (Perez-Reyes 1982)
    Strengths:
    - Biological finding
    - Both THC and metabolites were tested
    Minor limitations:

- No information about temporal relationship between use and presence in breast milk.
- Only two women were tested for presence of THC. Only one was tested for ratios between plasma and breast milk.
  - One baby's feces was tested, with much higher metabolite-to-THC proportion than was present in its mother's breast milk. (Perez-Reyes 1982)
  Strengths:
    - Biological finding
    - Both THC and metabolites were tested
  Limitations:
    - Could conversion to metabolites occur in the gut, without absorption?
    - Infant's urine was not tested.
    - Only one mother and child were tested.

We found <u>mixed</u> evidence for whether or not an association exists between maternal use of marijuana while breastfeeding and motor development in exposed infants.
  - Infants whose mothers used marijuana while breastfeeding during the first month of life (on at least 15 of 30 days) had poorer motor development at 1yr of age, but no significant difference in mental development (Astley 1990) *Medium quality evidence based on strengths and limitations.*
  - Infants whose mothers used marijuana while breastfeeding during the third month of life had no significant difference in mental or motor development at 1yr of age (Astley 1990) *Medium quality evidence based on strengths and limitations.*
  Strengths:
    - Longitudinal study - marijuana use during the 1st and 3rd month of lactation and follow up testing of infant at 1yr
    - Controls matched on multiple factors, including duration of lactation, prenatal marijuana exposure and month of birth
    - Marijuana exposure was a continuous variable (days exposed)
    - Good tools used to measure development at 1yr (Bayley Scales of Infant Development)
    - Adjusted for many variables - maternal age, race, income, education, marital status, pregnancy history, and weight gain; maternal tobacco, coffee, alcohol and other drug use during pregnancy or lactation; marijuana use during pregnancy; infant gestational age and sex
    - Mean change of a 12% decrease in scores
  Limitations:
    - Matching for prenatal marijuana exposure was unable to reduce the strong correlation between prenatal and lactation exposure (of women who reported marijuana use during pregnancy, 84% continued to use marijuana during lactation.
    - No confidence interval was given for the change
    - Mother-child interaction was not measured or adjusted for

- Infants whose mothers used marijuana while breastfeeding had no significant difference in mental or motor development at 1yr of age (Tennes 1985) Low *quality evidence based on strengths and limitations.*
  Strengths:
    - Longitudinal study
    - Good tools used to measure development at 1yr (Bayley Scales of Infant Development)
  Major limitations:
    - No statistics were given - mean, CI, etc., nor were statistical methods given. It was simply stated "Comparison of infant outcomes on growth, or on mental and motor development, revealed no apparent effects of postnatal marijuana exposure."
  Minor limitations:
    - Over 50% of "heavy users" were lost at 1 year.
    - Controls were chosen randomly from among non-exposed (not matched), and were demographically different from marijuana users
    - 62 total breastfeeding mothers, with only 6 who used marijuana more than weekly
    - Time period of exposure was not clarified - it appears to be any concurrent marijuana use and breastfeeding
    - Did not say anything about adjusting for potential confounding variables

We found <u>insufficient</u> evidence to determine whether or not infant exposure to marijuana (either from maternal marijuana use during breastfeeding or infant exposure to marijuana smoke) is associated with SIDS.
  - Infants exposed to marijuana postnatally did not have different risk of SIDS than those not exposed. (Klonoff-Cohen 2001) *Low quality evidence based on strengths and limitations.*
    Strengths:
      - Controls were matched on multiple factors
      - Cases and controls clearly defined
      - Adjusted for multiple potential confounders
    Major limitations:
      - Retrospective case-control study interviewing parents whose baby had died, about their drug use relative to the lost baby
      - Postnatal exposure defined as EITHER breastfeeding while using MJ, or exposing infant to marijuana smoke
    Minor limitations:
      - Reports "tremendous effort to locate" some cases, consisting of "14 strategies" - some might not have wanted to participate

      - Quantity of postnatal marijuana exposure not clarified - appears to be any vs. none
      - Wide confidence interval for OR (0.4-2.9)

References

1. Astley SJ, Little RE. Maternal marijuana use during lactation and infant development at one year. Neurotoxicol Teratol. 1990; 12(2):161-8.
2. Bada HS, Das A, Bauer CR, Shankaran S, Lester BM, Gard CC, et al. Low birth weight and preterm births: etiologic fraction attributable to prenatal drug exposure. J Perinatol. 2005;25(10):631-7.
3. Bluhm EC, Daniels J, Pollock BH, Olshan AF, States) CsOGU. Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States). Cancer Causes Control. 2006;17(5):663-9.
4. Cornelius MD, Goldschmidt L, Day NL, Larkby C. Alcohol, tobacco and marijuana use among pregnant teenagers: 6-year follow-up of offspring growth effects. Neurotoxicol Teratol. 2002;24(6):703-10.
5. D'Apolito K. Breastfeeding and substance abuse. Clin Obstet Gynecol. 2013;56(1):202-11.
6. Day NL, Goldschmidt L, Thomas CA. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. Addiction. 2006;101(9):1313-22.
7. Day NL, Leech SL, Goldschmidt L. The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. Neurotoxicol Teratol. 2011;33(1):129-36.
8. Day NL, Richardson GA, Goldschmidt L, Robles N, Taylor PM, Stoffer DS, et al. Effect of prenatal marijuana exposure on the cognitive development of offspring at age three. Neurotoxicol Teratol. 1994;16(2):169-75.
9. Day N, Cornelius M, Goldschmidt L, Richardson G, Robles N, Taylor P. The effects of prenatal tobacco and marijuana use on offspring growth from birth through 3 years of age. Neurotoxicol Teratol. 1992;14(6):407-14.
10. Day N, Sambamoorthi U, Taylor P, Richardson G, Robles N, Jhon Y, et al. Prenatal marijuana use and neonatal outcome. Neurotoxicol Teratol. 1991;13(3):329-34.
11. de Moraes Barros MC, Guinsburg R, de Araújo Peres C, Mitsuhiro S, Chalem E, Laranjeira RR. Exposure to marijuana during pregnancy alters neurobehavior in the early neonatal period. J Pediatr. 2006;149(6):781-7.
12. Dekker GA, Lee SY, North RA, McCowan LM, Simpson NA, Roberts CT. Risk factors for preterm birth in an international prospective cohort of nulliparous women. PLoS One. 2012;7(7):e39154.
13. Dreher MC, Nugent K, Hudgins R. Prenatal marijuana exposure and neonatal outcomes in Jamaica: an ethnographic study. Pediatrics. 1994;93(2):254-60.
14. El Marroun H, Hudziak JJ, Tiemeier H, Creemers H, Steegers EA, Jaddoe VW, et al. Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. Drug Alcohol Depend. 2011;118(2-3):470-4.
15. El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry. 2009;48(12):1173-81.

16.   El Marroun H, Tiemeier H, Steegers EA, Roos-Hesselink JW, Jaddoe VW, Hofman A, et al. A prospective study on intrauterine cannabis exposure and fetal blood flow. Early Hum Dev. 2010;86(4):231-6.

17.   English DR, Hulse GK, Milne E, Holman CD, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. Addiction. 1997;92(11):1553-60.

18.   Fergusson DM, Horwood LJ, Northstone K, Childhood ASTALSoPa. Maternal use of cannabis and pregnancy outcome. BJOG. 2002;109(1):21-7.

19.   Forrester MB, Merz RD. Comparison of trends in gastroschisis and prenatal illicit drug use rates. J Toxicol Environ Health A. 2006;69(13):1253-9.

20.   Forrester MB, Merz RD. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. J Toxicol Environ Health A. 2007;70(1):7-18.

21.   Fried PA, James DS, Watkinson B. Growth and pubertal milestones during adolescence in offspring prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol. 2001;23(5):431-6.

22.   Fried PA, O'Connell CM. A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. Neurotoxicol Teratol. 1987;9(2):79-85.

23.   Fried PA, Smith AM. A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. Neurotoxicol Teratol. 2001;23(1):1-11.

24.   Fried PA, Watkinson B. Differential effects on facets of attention in adolescents prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol. 2001;23(5):421-30.

25.   Fried PA, Watkinson B, Gray R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol. 1999;21(5):513-25.

26.   Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13- to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol. 2003;25(4):427-36.

27.   Fried PA, Watkinson B, Siegel LS. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. Neurotoxicol Teratol. 1997;19(3):171-83.

28.   Garry A, Rigourd V, Amirouche A, Fauroux V, Aubry S, Serreau R. Cannabis and breastfeeding. J Toxicol. 2009;2009:596149.

29.   Goldschmidt L, Day NL, Richardson GA. Effects of prenatal marijuana exposure on child behavior problems at age 10. Neurotoxicol Teratol. 2000;22(3):325-36.

30.   Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. Neurotoxicol Teratol. 2004;26(4):521-32.

31.   Goldschmidt L, Richardson GA, Willford JA, Severtson SG, Day NL. School achievement in 14-year-old youths prenatally exposed to marijuana. Neurotoxicol Teratol. 2012;34(1):161-7.

32.   Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. J Am Acad Child Adolesc Psychiatry. 2008;47(3):254-63.

33.   Gray KA, Day NL, Leech S, Richardson GA. Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. Neurotoxicol Teratol. 2005;27(3):439-48.

34.   Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. Clin Chem. 2010;56(9):1442-50.

35.   Hayatbakhsh MR, Flenady VJ, Gibbons KS, Kingsbury AM, Hurrion E, Mamun AA, et al. Birth outcomes associated with cannabis use before and during pregnancy. Pediatr Res. 2012;71(2):215-9.

36.   Hingson R, Alpert JJ, Day N, Dooling E, Kayne H, Morelock S, et al. Effects of maternal drinking and marijuana use on fetal growth and development. Pediatrics. 1982;70(4):539-46.

37.   Huizink AC. Prenatal cannabis exposure and infant outcomes: overview of studies. Prog Neuropsychopharmacol Biol Psychiatry. 2014;52:45-52.

38.   Hurd YL, Wang X, Anderson V, Beck O, Minkoff H, Dow-Edwards D. Marijuana impairs growth in mid-gestation fetuses. Neurotoxicol Teratol. 2005;27(2):221-9.

39.   Janisse JJ, Bailey BA, Ager J, Sokol RJ. Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth restriction. Subst Abus. 2014;35(1):60-7.

40.   Jaques SC, Kingsbury A, Henshcke P, Chomchai C, Clews S, Falconer J, et al. Cannabis, the pregnant woman and her child: weeding out the myths. J Perinatol. 2014;34(6):417-24.

41.   Jutras-Aswad D, DiNieri JA, Harkany T, Hurd YL. Neurobiological consequences of maternal cannabis on human fetal development and its neuropsychiatric outcome. Eur Arch Psychiatry Clin Neurosci. 2009;259(7):395-412.

42.   Kirksey A, Groziak SM. Maternal drug use: evaluation of risks to breast-fed infants. World Rev Nutr Diet. 1984;43:60-79.

43.   Klonoff-Cohen H, Lam-Kruglick P. Maternal and paternal recreational drug use and sudden infant death syndrome. Arch Pediatr Adolesc Med. 2001;155(7):765-70.

44.   Lester BM, Dreher M. Effects of marijuana use during pregnancy on newborn cry. Child Dev. 1989;60(4):765-71.

45.   Linn S, Schoenbaum SC, Monson RR, Rosner R, Stubblefield PC, Ryan KJ. The association of marijuana use with outcome of pregnancy. Am J Public Health. 1983;73(10):1161-4.

46.   Marchei E, Escuder D, Pallas CR, Garcia-Algar O, Gómez A, Friguls B, et al. Simultaneous analysis of frequently used licit and illicit psychoactive drugs in breast milk by liquid chromatography tandem mass spectrometry. J Pharm Biomed Anal. 2011;55(2):309-16.

47.   Moore DG, Turner JD, Parrott AC, Goodwin JE, Fulton SE, Min MO, et al. During pregnancy, recreational drug-using women stop taking ecstasy (3,4-methylenedioxy-N-methylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and cannabis: initial findings from the Development and Infancy Study. J Psychopharmacol. 2010;24(9):1403-10.

48.   Noland JS, Singer LT, Short EJ, Minnes S, Arendt RE, Kirchner HL, et al. Prenatal drug exposure and selective attention in preschoolers. Neurotoxicol Teratol. 2005;27(3):429-38.

49.   Perez-Reyes M, Wall ME. Presence of delta9-tetrahydrocannabinol in human milk. N Engl J Med. 1982;307(13):819-20.

50.   Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicol Teratol. 2005;27(2):267-77.

51.   Reisner SH, Eisenberg NH, Stahl B, Hauser GJ. Maternal medications and breast-feeding. Dev Pharmacol Ther. 1983;6(5):285-304.
52.   Richardson GA, Day N, Taylor PM. The Effect of Prenatal Alcohol, Marijuana, and Tobacco Exposure on Neonatal Behavior. Infant Behavior and Development. 1989;12:199-209.
53.   Riordan J, Riordan M. Drugs in breast milk. Am J Nurs. 1984;84(3):328-32.
54.   Roberson EK, Patrick WK, Hurwitz EL. Marijuana use and maternal experiences of severe nausea during pregnancy in Hawai'i. Hawaii J Med Public Health. 2014;73(9):283-7.
55.   Saurel-Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in 2010. BJOG. 2014.
56.   Schauberger CW, Newbury EJ, Colburn JM, Al-Hamadani M. Prevalence of illicit drug use in pregnant women in a Wisconsin private practice setting. Am J Obstet Gynecol. 2014.
57.   Schempf AH, Strobino DM. Illicit drug use and adverse birth outcomes: is it drugs or context? J Urban Health. 2008;85(6):858-73.
58.   Scragg RK, Mitchell EA, Ford RP, Thompson JM, Taylor BJ, Stewart AW. Maternal cannabis use in the sudden death syndrome. Acta Paediatr. 2001;90(1):57-60.
59.   Sharma P, Murthy P, Bharath MM. Chemistry, metabolism, and toxicology of cannabis: clinical implications. Iran J Psychiatry. 2012;7(4):149-56.
60.   Shaw GM, Velie EM, Morland KB. Parental recreational drug use and risk for neural tube defects. Am J Epidemiol. 1996;144(12):1155-60.
61.   Shiono PH, Klebanoff MA, Nugent RP, Cotch MF, Wilkins DG, Rollins DE, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. Am J Obstet Gynecol. 1995;172(1 Pt 1):19-27.
62.   Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. Neurotoxicol Teratol. 2004;26(4):533-42.
63.   Suarez L, Brender JD, Langlois PH, Zhan FB, Moody K. Maternal exposures to hazardous waste sites and industrial facilities and risk of neural tube defects in offspring. Ann Epidemiol. 2007;17(10):772-7.
64.   Tennes K, Avitable N, Blackard C, Boyles C, Hassoun B, Holmes L, et al. Marijuana: prenatal and postnatal exposure in the human. NIDA Res Monogr. 1985;59:48-60.
65.   United States Department of H, Human Services. Substance A, Mental Health Services Administration. Center for Behavioral Health S, Quality. National Survey on Drug Use and Health, 2013. 2014.
66.   van Gelder MM, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N, et al. Maternal periconceptional illicit drug use and the risk of congenital malformations. Epidemiology. 2009;20(1):60-6.
67.   van Gelder MM, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N, et al. Characteristics of pregnant illicit drug users and associations between cannabis use and perinatal outcome in a population-based study. Drug Alcohol Depend. 2010;109(1-3):243-7.
68.   Varner MW, Silver RM, Rowland Hogue CJ, Willinger M, Parker CB, Thorsten VR, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet Gynecol. 2014;123(1):113-25.

69.   Willford JA, Chandler LS, Goldschmidt L, Day NL. Effects of prenatal tobacco, alcohol and marijuana exposure on processing speed, visual-motor coordination, and interhemispheric transfer. Neurotoxicol Teratol. 2010;32(6):580-8.

70.   Williams LJ, Correa A, Rasmussen S. Maternal lifestyle factors and risk for ventricular septal defects. Birth Defects Res A Clin Mol Teratol. 2004;70(2):59-64.

71.   Williams SM, Mitchell EA, Taylor BJ. Are risk factors for sudden infant death syndrome different at night? Arch Dis Child. 2002;87(4):274-8.

72.   Zammit S, Thomas K, Thompson A, Horwood J, Menezes P, Gunnell D, et al. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. Br J Psychiatry. 2009;195(4):294-300.

Unintentional Marijuana Exposures in Children

Evidence Summary

COLORADO
Department of Public
Health & Environment

Evidence Summary: Unintentional Marijuana Exposures in Children
Presented to the Retail Marijuana Public Health Advisory Committee January 12, 2015

We found moderate evidence that more unintentional marijuana exposures of children occur in states with increased legal access to marijuana; and the exposures can lead to significant clinical effects requiring medical attention.

- There was an increase in unintentional MJ poisonings in children seen at the emergency department after modification of drug enforcement laws for marijuana possession in Colorado (Wang 2013) *Medium quality finding based on strengths and limitations*
- There was a significant increase in poison center for unintentional MJ ingestions in children seen from 2005 to 2011 in states that legalized medical marijuana. There was also a significant difference between the rate of calls between states that legalized medical marijuana compared with non-legal states. (Wang 2014) *Medium quality finding based on strengths and limitations*

- Wang 2013
    - o There was an increase in unintentional MJ poisonings in children seen at the emergency department after modification of drug enforcement laws for marijuana possession (Wang 2013) *Medium quality finding based on strengths and limitations*
      Strengths:
        - ▪ Ecological (retrospective) study based on ICD-9 coding for a tertiary-care, freestanding children's hospital emergency department in Colorado
        - ▪ Compared multi-year periods before and after modification of federal drug enforcement laws of marijuana possession in the state
        - ▪ 790 and 588 unintentional ingestions (of any substance) were reviewed in the two periods studied
        - ▪ MJ exposure confirmed by urine toxicology
      Minor limitations:
        - ▪ A single medical record reviewer was not blind to group, however an objective measure (urine toxicology) was the primary criteria used
        - ▪ Hospital practices, including urine testing for MJ, may have been different between the two periods
        - ▪ May have missed patients not captured by ICD-9 coding.

- Wang 2014
    - o There was a significant increase in poison center for unintentional MJ ingestions in children seen from 2005 to 2011 in states that legalized medical marijuana. There was also a significant difference between the rate of calls between states that legalized medical marijuana compared with non-legal states. (Wang 2014) *Medium quality finding based on strengths and limitations*
      Strengths:

- Ecological (retrospective) study using US national level data from the American Association of Poison Control Centers Data, over a 7 year period
- Only single-substance exposures were studied
- States level comparisons, grouped by MJ legalization before 2005, from 2005 to 2011, and no legalization

Minor limitations:
- Not all exposures may be reported to poison centers
- Exposures were not necessarily confirmed with biologic testing
- Poison center practices between states might be different, for example, sensitivity to MJ exposure in MJ legalized states might be highest

We found moderate evidence that use of child-resistant packaging reduces unintentional pediatric poisonings from a wide range of hazardous household products including pharmaceutical products.

- Accidental poisonings from prescription drugs in children under six were reduced 91% by the introduction of "Palm-N-Turn" container with a child resistant cap. Of the 88 remaining ingestions, 25% (22) were due to product failure – child was able to pry open or destroy the cap of the container. 33% (29) cases were due to incomplete cap replacement - 19 %(17) were due to cap being left off, and remaining 20% (20) were due to transfer of product to alternate container. (Breault 1974) *Medium quality finding based on strengths and limitations*

- There was a 34% reduction in the aspirin-related child (<5 years) mortality rate following the implementation of child-resistant packaging regulations. (Rodgers, 2002) *Medium quality finding based on strengths and limitations*

- Clarke and colleagues review the data on aspirin (both baby and adult dose) poisonings in children under five and attribute a 43% decrease in accidental poisonings in the three year period studied to the introduction of child resistant caps. (Clarke, 1979) *Low quality finding based on strengths and limitations*

- Breault, 1974
  - Accidental poisonings from prescription drugs in children under six were reduced 91% by the introduction of "Palm-N-Turn" container with a child resistant cap. Of the 88 remaining ingestions, 25% (22) were due to product failure – child was able to pry open or destroy the cap of the container. 33% (29) cases were due to incomplete cap replacement - 19%(17) were due to cap being left off, and remaining 23% (20) were due to transfer of product to alternate container. (Breault 1974) *Medium quality finding based on strengths and limitations*

    Strengths:
    - Ecological (retrospective) study using regional data with almost complete participation from reporting parties. Data collected over a five year period

Limitations:
- Outcome variable is "prescription drug ingestion, poisonings per day" reported to a single Poison Control Center representing the county. Likely underestimates the actual number of incidents related to ingestions some of which would be captured by local emergency departments.
- No local control group – other poison centers in the area did not collect age- specific data.

- Rodgers, 2002
  - There was a 34% reduction in the aspirin-related child (<5 years) mortality rate following the implementation of child-resistant packaging regulations. (Rodgers, 2002) *Medium quality finding based on strengths and limitations*
    Strengths:
    - Ecological (retrospective) study using National Center on Health Statistics death data for the years 1958 through 1990
    - Modeled expected annual number of poisoning-related child deaths, assuming negative binomial distribution. Adjusted for variables including changes in ED services, increased safety awareness of parents, and identification of relationship between aspirin use in children and Reye's syndrome.
    Limitations:
    - No adjustment for possible changes in use patterns of children's aspirin.
    - No adjustment for changes in bottle size requirements for children's aspirin.

- Clarke, 1979
  - Clarke and colleagues review the data on aspirin (both baby and adult dose) poisonings in children under five and attribute a 43% decrease in accidental poisonings in the three year period studied to the introduction of child resistant caps. (Clarke, 1979) *Low quality finding based on strengths and limitations*
    Strengths:
    - Pre-intervention/post-intervention analysis using Poison Control Centers (PCC) and National Center on Health Statistics death data.
    - Adjustments for change in population of children less than five, and change in demand for aspirin (substitutions available).
    - Analyze the baby aspirin and adult aspirin data separately.
    Limitations:
    - Authors notes some childhood deaths are related to therapeutic overdose.
    - No data on sales of aspirin substitutes.

References:

Breault HJ. Five years with 5 million child-resistant containers. Clin Toxicol. 1974;7(1):91-5.

Clarke A, Walton WW: Effect of safety packaging on aspirin ingestion by children. Pediatrics. 1979;63:687-693.

Rodgers GB: The Effectiveness of Child-Resistant Packaging for Aspirin. Archives of Pediatric and Adolescent Medicine. 2002;156:929-33.

Wang GS, Roosevelt G, Heard K. Pediatric marijuana exposures in a medical marijuana state. JAMA Pediatrics. 2013 Jul;(167(7)630-3.

Wang GS, et. al., Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. Annals of Emergency Medicine. 2014;63(6)684-9.

Marijuana Use Among Adolescents and Young Adults

Evidence Summary

COLORADO
Department of Public
Health & Environment

DEFINTIONS:

Age Groups:
- Adolescents: 9 through 17 years of age
- Young adults: 18 through 24 years of age

Levels of Marijuana Use
- Heavy marijuana use: daily or near daily (5-7 days/week)
- Regular marijuana use: weekly (1-4 days/week)
- Occasional marijuana use: less than weekly
- Acute marijuana use: Used within the last hour.
- Any level of use: evidence for all of the above

We found moderate evidence that adolescents and young adults who regularly use marijuana are more likely than non-users to have ongoing impairment of cognitive and academic abilities for at least 28 days after last use
- Marijuana users who started before age 17 and had used "heavily" (Committee's definition of "regularly") had significant impairment in verbal memory and association compared with non-users, after at least 28 days abstinence (Pope 2003) *Medium quality evidence based on strengths and limitations*
- Amount of marijuana used is linearly associated with worse performance in verbal memory, visual learning, executive functioning, psychomotor speed, complex reaction time and manual dexterity, even after 30 days abstinence (Bolla 2002) *Medium quality evidence based on strengths and limitations*
- Adolescents with greater lifetime use of marijuana had significantly lower scores on verbal memory & learning, executive function, and sequencing ability than non-users after 28 days of abstinence (Medina 2007) *Medium quality evidence based on strengths and limitations*
- Adolescent marijuana users abstinent at least 30 days had significantly worse performance on reading and math achievement tests than non-users (Hooper 2014) *Medium quality evidence based on strengths and limitations*
- No significant difference was found in attention, memory, executive function or IQ between adolescent marijuana users abstinent at least 30 days and non-users (Hooper 2014) *Low quality evidence based on strengths and limitations*

We found limited evidence that adolescents who regularly use marijuana are more likely than non-users to score lower on IQ tests 12 hours or more after last use
- Adolescents with current heavy marijuana use have significant impairment in immediate memory, general memory, IQ and processing speed, after a brief abstinence (Fried 2005) *Low quality evidence based on strengths and limitations*
- Persistent, "heavy" users (Committee definition of "regular" user) users who started by age 18 had a drop in IQ from childhood to age 38. (Meier 2012) *Low quality evidence based on strengths and limitations*
- Adolescents with heavy marijuana use had significantly lower IQ scores than non-users, after a brief abstinence -- Extent of adolescent marijuana use (uses per

week) was linearly related to decreases in IQ scores after a brief abstinence (Fried 2002) *Low quality evidence based on strengths and limitations*

We found moderate evidence that adolescents who regularly use marijuana are less likely than non-users to graduate from high school

- Adolescents' likelihood to graduate high-school decreased with greater total marijuana use before age 16 (Fergusson 2003) *Medium quality evidence based on strengths and limitations*
- Youth using marijuana in high-school had significantly lower high school graduation rates than non-users (Lynne-Landsman 2010) *Low quality evidence based on strengths and limitations*
- Adolescent marijuana users were less likely to proceed beyond 11th grade than non-users (Brook 1999) *Low quality evidence based on strengths and limitations*

We found limited evidence that adolescents who regularly use marijuana are less likely than adolescent non-users to attain a college degree

- Total adolescent use of marijuana was significantly associated with less university degree attainment, lower income, higher unemployment, and higher welfare dependence, all with a dose response (Fergusson 2008) *Medium quality evidence based on strengths and limitations*
- Adolescents who started using marijuana at a younger age were significantly less likely to complete high school, enroll in university or attain a university degree than those who started at a later age or did not start -- Young adults who used marijuana more frequently were significantly less likely to complete high school, enroll in university or attain a university degree than those who used less frequently or did not use (Horwood 2010) *Medium quality evidence based on strengths and limitations*
- No significant relationship was found between young adults' likelihood to attain a university degree by age 25 and total marijuana use before age 20 (Fergusson 2000) *Low quality evidence based on strengths and limitations*

We found moderate evidence that adolescent and young adult marijuana users are more likely than non-users to increase their use and to become addicted to marijuana in adulthood

- Adolescents using marijuana at any level were significantly more likely to be addicted at age 24 than non-using adolescents, and the odds of addiction at 24 increased with higher adolescent use (Swift 2008) *Medium quality evidence based on strengths and limitations*
- Adolescents using marijuana only occasionally (never used regularly) before age 18 were significantly more likely to use regularly at age 24 compared with adolescent non-users, and significantly more likely to be addicted at age 24 (Swift 2008) *Medium quality evidence based on strengths and limitations*
- Youth using marijuana in high school were significantly more likely to meet criteria for marijuana abuse or dependence at age 21 than non-users (Lynne-Landsman 2010) *Low quality evidence based on strengths and limitations*

- Adolescent marijuana users were more likely to report problem use of marijuana than non-users (Brook 1999) *Low quality evidence based on strengths and limitations*

We found moderate evidence that adolescent and young adult marijuana users are more likely than non-users to use and be addicted to alcohol or tobacco in adulthood
- Young adults who used marijuana occasionally but not regularly were more likely to use tobacco, more likely to use amphetamines, more likely to use cocaine, more likely to use ecstasy and more likely to have high-risk alcohol use 4-5 years later (Swift 2012) *Medium quality evidence based on strengths and limitations*
- Youth using marijuana in high-school were significantly more likely at age 21 to meet criteria for alcohol abuse, and to use other illicit drugs, than non-users (Lynne-Landsman 2010) *Low quality evidence based on strengths and limitations*
- Adolescent marijuana users were more likely to report problem use of alcohol and more likely to report problem use of tobacco than non-users (Brook 1999) *Low quality evidence based on strengths and limitations*

We found substantial evidence that adolescent and young adult marijuana users are more likely than non-users to use and be addicted to illicit drugs in adulthood
- Young adults who used marijuana occasionally but not regularly were more likely to use tobacco, more likely to use amphetamines, more likely to use cocaine, more likely to use ecstasy and more likely to have high-risk alcohol use 4-5 years later (Swift 2012) *Medium quality evidence based on strengths and limitations*
- Adolescents who used marijuana more frequently were more likely to use other illicit drugs, to meet criteria for abuse/dependence on other drugs, and to use a greater number of other types of drugs (Fergusson 2006) *Medium quality evidence based on strengths and limitations*
- Individuals who used marijuana as adolescents had significantly higher likelihood of using other illicit drugs compared with non-users, and that likelihood was higher with more marijuana use (Fergusson 2000) *Medium quality evidence based on strengths and limitations*
- Adolescents who misused prescription medications within the past year were significantly more likely to have used marijuana in the past year -- Adolescents who exhibited symptoms of prescription drug abuse or dependence within the past year were significantly more likely to have used marijuana in the past year (Schepsis 2008) *Low quality evidence based on strengths and limitations*
- Youth using marijuana in high-school were significantly more likely at age 21 to meet criteria for alcohol abuse, and to use other illicit drugs, than non-users (Lynne-Landsman 2010) *Low quality evidence based on strengths and limitations*
- Young adults who used marijuana prior to age 18 were significantly more likely to later use opiate medicines without a prescription, whether men or women (Fiellin 2013) *Low quality evidence based on strengths and limitations*
- Adolescents who 'recently' started using opiates or stimulants were significantly more likely to have used marijuana at a prior time (compared with those who didn't recently start using opiates or stimulants), and the relationship was stronger

for those who continued using marijuana than for those who stopped (Nakawaki 2012) *Low quality evidence based on strengths and limitations*

- Adolescents who used marijuana but not alcohol or tobacco in high school or before were significantly more likely (than non-users) to use cocaine, crystal meth, and other illegal drugs 14 years later -- Adolescents who used marijuana and alcohol in high school or before were significantly more likely (than alcohol users who didn't use marijuana) to use non-prescribed prescription meds, cocaine, crystal meth, and other illegal drugs 14 years later -- Adolescents who used marijuana and tobacco in high school or before were significantly more likely (than tobacco users who didn't use marijuana) to use sedatives, tranquilizers, cocaine, and other illegal drugs 14 years later -- Adolescents who used marijuana, alcohol and tobacco in high school or before were significantly more likely (than alcohol and tobacco users who didn't use marijuana) to use sedatives, cocaine, and crystal meth 14 years later (Moss 2014) *Low quality evidence based on strengths and limitations*

We found mixed evidence for whether or not adolescent and young adult marijuana users are more likely than non-users to have symptoms or diagnosis of anxiety in adulthood

- Adolescent girls who used marijuana, compared with non-users, were significantly more likely to require hospital treatment for depression or anxiety by age 25 (Miettunen 2013) *Medium quality evidence based on strengths and limitations*
- Adolescents who used marijuana regularly were significantly more likely than non-users to suffer anxiety at age 29 (Degenhardt 2013) *Low quality evidence based on strengths and limitations*
- No significant relationship was found between adolescent boys who used marijuana and occurrence of hospital treatment for depression or anxiety by age 25, compared with non-users (Miettunen 2013) *Low quality evidence based on strengths and limitations*

We found mixed evidence for whether or not adolescent and young adult marijuana users are more likely than non-users to have symptoms or a diagnosis of depression in adulthood

- Adolescent and young adult marijuana users were more likely to suffer depression, and the effect increases with greater frequency of marijuana use (Horwood 2012) *Medium quality evidence based on strengths and limitations*
- Adolescent girls who used marijuana, compared with non-users, were significantly more likely to require hospital treatment for depression or anxiety by age 25 (Miettunen 2013) *Medium quality evidence based on strengths and limitations*
- No significant relationship was found between marijuana use in adolescence and depressive symptoms at age 26 (Arseneault 2004) *Medium quality evidence based on strengths and limitations*
- No significant difference in depression at age 29 was seen between adolescent marijuana users and non-users (Degenhardt 2013) *Medium quality evidence based on strengths and limitations*

- Teen women who used marijuana and continued to use in their 20's were more likely to have depression and anger/hostility by age 32 than non-users, while no significant difference was found between teen women who had used and quit using, compared with non-users (Pahl 2011) *Low quality evidence based on strengths and limitations*
- Adolescents who used marijuana but not other drugs were more likely to have depression two years later, and that likelihood was higher with greater marijuana use (Rasic 2013) *Low quality evidence based on strengths and limitations*
- No significant relationship was found between adolescent boys who used marijuana and occurrence of hospital treatment for depression or anxiety by age 25, compared with non-users (Miettunen 2013) *Low quality evidence based on strengths and limitations*

We found mixed evidence for whether or not adolescent and young adult marijuana users are more likely than non-users to have suicidal thoughts or attempt suicide
- 15-16 year old marijuana users were significantly more likely to have attempted suicide than non-users (Kokkevi 2012) *Low quality evidence based on strengths and limitations*
- Both adolescent boys and girls who used marijuana were significantly more likely to have had a suicide attempt (Consoli 2013) *Low quality evidence based on strengths and limitations*
- No significant difference was found between adolescents who used marijuana but not other drugs, compared with non-users, in the likelihood of suicide ideation or attempt two years later (Rasic 2013) *Medium quality evidence based on strengths and limitations*
- No significant relationship was found between marijuana use in adolescents and later self-harm (Spears 2014) *Low quality evidence based on strengths and limitations*

We found substantial evidence that adolescents and young adults who regularly use marijuana are more likely than non-users to develop psychotic symptoms or psychotic disorders like schizophrenia in adulthood.
- Adolescent and young adult marijuana users were more likely to develop psychotic symptoms, and that likelihood was higher with greater marijuana use, while psychotic symptoms did not lead to marijuana use (Fergusson 2005) *Medium quality evidence based on strengths and limitations*
- Males who used marijuana in adolescence were significantly more likely to develop schizophrenia in later years, and that likelihood was higher with greater marijuana use (Zammit 2002) *Medium quality evidence based on strengths and limitations*
- Marijuana users who started using as teens had significantly more schizophrenia symptoms at age 26 than those who had not started by age 18, with the greatest impact among those who started by age 15 (Arseneault 2004) *Medium quality evidence based on strengths and limitations*
- Marijuana users were more likely to develop psychosis symptoms, and more likely to develop a psychotic disorder requiring treatment, than non-users, and that

likelihood was higher with greater marijuana use (van Os 2002) *Low quality evidence based on strengths and limitations*

- Adolescent marijuana users were more likely to experience psychotic symptoms in later years (Kuepper 2011) *Low quality evidence based on strengths and limitations*
- Adolescents with a predisposition to psychosis who use marijuana are significantly more likely to have psychotic symptoms in later years than non-users (Henquet 2005) *Low quality evidence based on strengths and limitations*

We found moderate evidence that adolescent and young adult marijuana users who quit have lower risks of cognitive and mental health outcomes than those who continue to use

- Adolescent marijuana users who quit using marijuana were significantly less likely to later use amphetamines, cocaine or ecstasy than adolescent marijuana users who continued to use marijuana (Swift 2012) *Medium quality evidence based on strengths and limitations*
- No significant difference was found between former marijuana using adolescents and non-users in immediate memory, general memory, IQ or processing speed (Fried 2005)   *Low quality evidence based on strengths and limitations*
- No significant difference was found between former marijuana using adolescents and non-users in IQ (Fried 2002)   *Low quality evidence based on strengths and limitations*
- Teen women who used marijuana and continued to use in their 20's were more likely to have depression and anger/hostility by age 32 than non-users, while no significant difference was found between teen women who had used and quit using, compared with non-users (Pahl 2011) *Low quality evidence based on strengths and limitations*

STUDY FINDINGS, STRENGTHS AND LIMITATIONS
Arseneault 2004
  Strengths:
- Longitudinal study in the Dunedin birth cohort, with 759 subjects
- Analyzed groups of marijuana users who started by age 15 or by age 18
- Adjusted for psychotic symptoms at age 11, socioeconomic status, gender, and non-marijuana drug use
- Marijuana use by age 15 led to more than 6 point increase on a 58 point scale of symptoms
- Inclusion of non-marijuana drug use in the regression model showed that non-marijuana drug use had no effect on schizophrenia symptoms (the increase was all due to marijuana)
  Minor limitations:
- Marijuana users defined as having used three times or more
- Did not assess or adjust for psychotic symptoms at 15 or 18 year ages
- Did not adjust for alcohol use

- Marijuana use by age 18 led to only a 1 point increase on a 58 point scale of symptoms
- Schizophreniform disorder was also analyzed, and the results were not significant between teen marijuana use and the disorder at age 26, likely due to insufficient power (CI 0.73-13.29 for users by age 15, 0.54-3.74 for users by age 18)

Becker 2014

Strengths:
- 73 subjects 18-20 years old
- Heavy marijuana users and non-users were compared
- Excluded for daily tobacco use or heavy alcohol use
- Abstained for 12 hours prior to testing
- Adjusted for gender, IQ and alcohol use
- Rey Auditory Verbal Learning Test, Spatial Delayed Response Task and Iowa Gambling Task, all validated instruments, measured these domains

Minor limitations;
- Did not adjust for other social or personal factors that could affect performance
- Did not assess regular or occasional users
- Motor function, processing speed, verbal fluency, and attention were tested with no impairment

Block 1990

Strengths:
- 191 subjects who started using marijuana around 10th grade
- Scores on fourth-grade Iowa Tests of Basic Skills were obtained for comparison
- Heavy use and regular use were evaluated separately
- Requested abstinence for 24 hours prior to testing

Minor limitations:
- The "nonusers" group appears to include occasional use (anything less than once weekly)
- There was a difference in performance on one subtest related to language skills, and the authors point out that the marijuana users had lower scores on language skills in fourth-grade, but results were not actually adjusted for fourth-grade scores
- Additional testing was described in the methods section, but not addressed in results

Bolla 2002

Strengths:
- Marijuana use measured as joints per week, to better quantify the amount of use than other methods (group means were about 10, 40 & 90)
- Results show a dose response

- Subjects excluded for drug or alcohol dependence other than marijuana, psychiatric disorder, neurological illness or trauma, or abnormal neurologic exam
- Subjects admitted for 30 days of monitored abstinence
- Examiner was blinded to subjects' group assignments
- Adjusted for age, gender, education, depression score and IQ

Minor limitations:
- Cross-sectional
- Age ranged from 18 up, with mean age of 22
- 22 subjects with varying amount of use, no controls
- 15 tests were performed, scores on 7 had a negative correlation with amount of use, but the other 8 did not
- Not adjusted for alcohol use

Brook 1999

Strengths:
- Longitudinal study over 5 years from early to late adolescence (mean age 14 at baseline)
- Marijuana use at baseline was compared with outcomes 5 years later
- Adjusted for age, gender and ethnicity
- Education attainment adjusted for education at baseline

Minor limitations:
- Only included African American and Puerto Rican youth in East Harlem
- Marijuana use was dichotomized to either once a month or more often, vs less than once a month
- Number of subjects in the 'marijuana use' group was not given, and since it was assessed at mean age 14, it could have been small
- Drug problems were assessed with a simple question of subjects "Have you ever had a problem with -x-?"

Consoli 2013

Strengths:
- Survey of 36,757 17-year olds, representing all French 17-year olds
- Of 44,733 invited, 88.4% participated
- Adjusted for educational level, repeated school years, SES, alcohol use, tobacco use, living with parents, parental separation and harmony, and quality of relationship with mother and father
- Stratified by gender
- Overall marijuana use and outcome rates were given (13.5% used marijuana, and 8.2% had a suicide attempt)

Major limitations:
- Cross-sectional study with suicide attempts measured as any lifetime, while marijuana use was current

Minor limitations:

- One category of marijuana use - 10 times or more per year

Degenhardt 2013
   Strengths:
- Longitudinal study over 15 years, with 9 time-points
- Sample selected by cluster randomization from all schools in Victoria, Australia
- 1943 subjects starting in 9th grade
- 98% of adolescents in Victoria who should be attending school in 9th grade were, and thus were potential subjects
- Marijuana use categories were none, occasional, or regular/heavy
- Depression and anxiety were measured at age 29 using the Composite International Diagnostic Interview, which identifies DSM-IV criteria
- Adjusted for gender, urban/rural, cigarette smoking, alcohol use, other drug use, parental divorce, and parental HS completion
   Minor limitations:
- 22% of the initial participants were not interviewed at the final time-point, including 14% who refused and 8% with lost contact
- Though randomly selected, the cluster method could have resulted in subject groups that are different from the general population
- When adjusted for adolescent depression/anxiety, the relationship between adolescent marijuana use and later anxiety was no longer significant, but such adjustment could be over adjustment - the timing of adolescent marijuana use and adolescent depression/anxiety is not clear

Fergusson 2000
   Strengths:
- Longitudinal birth cohort study to age 21
- 1265 children born in Christchurch, New Zealand
- Use was divided into number of times per year, with the highest frequency category being 50+ times (roughly weekly, or regular use)
- Adjusted for gender, IQ, tobacco use, alcohol use, juvenile violence or property offenses, school dropout, conduct problems, attitudes to drug use, peer drug use, novelty seeking, risk taking, parental use of physical punishment, childhood sexual abuse, adverse life events, parental attachment, family SES, parental divorce/death/other changes, parental conflict, parental alcohol problems, parental criminality, and parental illicit drug use
- 89% of original sample members alive and living in New Zealand were included to the end of the study, and attrition analysis showed small differences
- Over 25% of subjects had used a non-marijuana illicit drug by age 21
- Supplementary analysis looked at each illicit drug individually (opiates, cocaine, hallucinogens, solvents and prescription drugs), with all being highly significant
- 99% of those who used non-marijuana illicit drugs had used marijuana prior

Major limitations
- ▪ It appears that hazard ratios were calculated based on marijuana use in the same year as other drug use, not marijuana use prior to other drug use

Minor limitations:
- ▪ Marijuana use was recorded in one-year periods, but after age 16, interviews were only done at 18 and 21, with questions about marijuana requiring 2-3 years recall

Fergusson 2003

Strengths:
- ▪ Longitudinal birth cohort study to age 25
- ▪ 1265 children born in Christchurch, New Zealand
- ▪ Marijuana use categories were calculated for total marijuana use within certain age ranges (14-16 years of age, 14-18, and 14-20), as never used, used 1-9 times, 10-99 times, or 100+ times
- ▪ Total marijuana use from 14-16 years of age was compared with completing high-school, 14-18 was compared with entering university study, and 14-20 was compared with attaining a university degree
- ▪ Adjusted for gender, cognitive and scholastic ability, reading comprehension, mathematical reasoning, tobacco use, behavior or conduct problems, novelty seeking, peer deviance, maternal education, maternal age at birth, parental attachment or changes in parents, childhood physical or sexual abuse, family SES, parental alcohol problems, parental criminality, and parental illicit drug use
- ▪ High-school drop-out showed a dose response and clear statistical significance (OR for 100+ uses 3.7, CI 1.8-7.5)

Minor limitations:
- ▪ Marijuana use was recorded in one-year periods, but after age 16, interviews were only done at 18 and 21, with questions about marijuana requiring 2-3 years recall
- ▪ The maximum marijuana use category includes less than weekly use (compare with 2008 analysis of the same cohort, with max marijuana use category of 400+ times)
- ▪ Only 11 subjects in the maximum marijuana use group from 14-16 years age
- ▪ Entering university had a wide confidence interval (OR for 100+ uses of marijuana was 0.82, CI 0.5-1.3)
- ▪ Attaining a university degree had a CI just crossing 1 for all marijuana use categories (OR for 100+ uses 0.68, CI 0.5-1.0)

Fergusson 2005

Strengths:
- ▪ Longitudinal birth cohort study to age 25
- ▪ 1055 subjects born in Christchurch, New Zealand had information on marijuana use and psychotic symptoms available for final analysis
- ▪ Marijuana use was divided into categories, with the highest frequency category being daily use

- Psychotic symptoms were analyzed using a scaled (ordinal) score
- Adjusted for gender, IQ, tobacco use, alcohol use, neuroticism, novelty seeking, self-esteem, peer deviance, maternal education, maternal age at birth, parental attachment or changes in parents, childhood physical or sexual abuse, adverse life events, family SES and living standards, parental depression or anxiety, parental alcohol problems, parental criminality, and parental illicit drug use
- Structural modeling was used to analyze reciprocal effects of marijuana use and psychotic symptoms, showing marijuana use increased psychotic symptoms but symptoms did not increase marijuana use

Minor limitations:
- Marijuana use was concurrent with psychotic symptoms in the regression analysis, and the description of structural modeling was too technically complex to understand how it corrected for this
- Assessments for this study were at ages 18, 21 and 25, not younger

Fergusson 2006

Strengths:
- Same data and strengths as Fergusson 2000, plus another time point at age 25
- Regression analysis was done to identify linear relationship rather than categorical odds ratios

Major limitations:
- Analysis was still done comparing marijuana use and other drug use in the same year

Minor limitations:
- Same limitations as Fergusson 2000

Fergusson 2008

Strengths:
- Longitudinal birth cohort study to age 25
- 1265 children born in Christchurch, New Zealand
- Marijuana use was summed for reported number of uses on all surveys from age 14 to 21, giving an approximate total cannabis use variable, categorized into 6 groups from no use to 400+ lifetime uses
- The smallest number of subjects in any category of use was 44
- Results were confirmed by analysis using alternate marijuana use measures - one was frequency of use (instead of total use), and the other was total use from age 14-18 (excluding use from 19-21)
- Adjusted for cognitive ability and grade average, tobacco use, alcohol use, other drug use, conduct and attention problems, major depression, peer drug use and crime, parental use of physical punishment, childhood sexual abuse, parental attachment, family SES, living standards and measures of adversity, maternal age and education, parental divorce/death/other changes, parental alcohol problems, parental criminality, and parental drug use

- The Intimate Relations Scale was previously validated

Minor limitations:
- 79% of original cohort had information through age 25
- The questions for life satisfaction were not previously validated, and no assessment of validity in this study is given
- Both life satisfaction and relationship satisfaction scores were on ordinal scales, with change of 2-3 points for maximum marijuana use (400+ times) from scores for never users of approximately 20 and 26 - it's difficult to determine the 'clinical significance' of these scores

Fiellin 2013

Strengths:
- Used pooled data from 3 years of the National Survey on Drug Use and Health, a broad U.S. focused survey
- Included 55,215 subjects 18-25 years old
- Analyzed four age groups individually 18-19, 20-21, 22-23 and 24-25
- Used age of first use of marijuana, alcohol or tobacco, compared with current opiate use, to analyze the temporal relationship
- Adjusted marijuana results for age, gender, race, alcohol and tobacco use
- Results were stratified and reported separately by gender
- Tight confidence intervals far from 1

Minor limitations:
- Cross-sectional study
- Amount of marijuana use is not assessed, only age of first use is analyzed
- The definition of opiate use is ever vs never
- Not adjusted for many family, social or personal factors that other studies have found to be related to substance use

Fried 2002

Strengths:
- Longitudinal study from a birth cohort in Ottawa
- 70 subjects with urinalysis results at age 17-20 and IQ testing at both 9-12 and 17-20
- Subjects had no past 'hard drug use' by self-report, confirmed at age 17-20 by urinalysis
- Marijuana use categories were based on correlation of self-report with urine THC metabolite levels, into heavy, regular, or 'non-users'
- Adjusted for age, gender, tobacco use, alcohol use, secondhand marijuana exposure, education level, family income, parental education, mother's age at subject's birth and use of tobacco, alcohol or marijuana during pregnancy

Minor limitations:
- 'Non-users' definition (less than weekly use) could have included occasional users
- Former marijuana use amounts were not clear for the 'former users' group

- Difference in IQ scores using number of joints as a continuous variable was very small (-0.24 points/joint), and analysis with use as categorical (heavy, regular and 'non-users') showed difference only for heavy use
- Drug abstinence unclear - stated as 'it is unlikely that the subjects were assessed while in an acute state of intoxication.'

Fried 2005

Strengths:
- Longitudinal birth cohort study in Ottawa, this study using testing and information on 113 subjects from age 9-12 and age 17-21
- Cognitive tests were done at both age ranges, allowing analysis of within-subject differences - all results adjusted for performance at age 9-12
- Excluded for any drug use other than marijuana, tobacco or alcohol
- Marijuana use categories of occasional/regular, heavy, former and non-users
- Adjusted for age, gender, tobacco use, alcohol use, family income, parental education, maternal substance use during pregnancy and DSM criteria for various psychiatric disorders (depression, anxiety, ADHD, conduct disorder, alcohol abuse or dependence, oppositional defiant disorder or dysthymic disorder)

Minor limitations:
- Former marijuana use amounts were not clear for the 'former users' group
- Values for groupwise comparisons were not given, just an ANCOVA table and statements in the text about heavy use vs control
- Self-reported abstinence 'on day of testing' makes duration unclear

Henquet 2005

Strengths:
- Longitudinal study of 2437 subjects age 14-24 years, randomly selected in Munich from the population registry
- Definition of psychotic symptoms was narrowed (compared with Kuepper study) to 'yes' on two psychosis items on the CIDI
- Adjusted for age, gender, SES, use of other drugs, childhood trauma, urban/rural, tobacco, alcohol, other drugs and symptoms of depression
- Analysis done stratifying for 'predisposition to psychosis' (symptoms at baseline) showed that risk of later symptoms was doubled for marijuana users vs. non-users among those with 'predisposition'

Minor limitations:
- Marijuana use was simply 5 or more times prior to baseline
- Assessment of psychosis symptoms were done at follow-up but asked about any lifetime symptoms
- No significant difference was found in psychotic symptoms at follow-up between marijuana users and non-users, among individuals without 'predisposition'

Hooper 2014
    Strengths:
    - 103 adolescent subjects, mean age 16
    - Excluded for medical, neurological, developmental or psychotic disorders, head injury, birth complications or maternal substance use during pregnancy, very low IQ
    - Abstinence at least 1 month at time of testing
    - Adjusted for age, gender, race, SES, parental IQ, child protective services history, ADHD and conduct disorder
    - Urine and saliva tests done day of testing for any drugs
    Minor limitations:
    - Scores in attention, memory, executive function and IQ were lower for users, and although they weren't significant, CI's and p-values weren't given
    - Users were adolescents who had previously received treatment for cannabis use disorder

Horwood 2010
    Strengths:
    - Pooled data from three longitudinal studies in Australia and New Zealand - CHDS, VAHCS and MUSP, with over 6000 total subjects
    - Three categories for age of marijuana use onset were used - 14 or younger, 15-17, and never used before 18
    - Frequency of marijuana use varied from never to daily (heavy use)
    - Adjusted for various measures of family SES, child cognitive ability, family functioning, and child/early adolescent behavioral adjustment
    - Both age of onset and frequency of use showed progressive relationship, with younger age at onset or more frequent use linked with less achievement
    Minor limitations:
    - The measures of 'frequency of marijuana use' used data are from age 21
    - Adjusted factors were different for the three studies, but all had multiple relevant covariates analyzed
    - Results from the three studies were different in magnitude, but all were statistically significant and in the same direction of effect
    - Group comparisons used 'age of onset under 15' and 'daily use' as the reference groups, thus p-values are not available for comparisons between 'never before 18' vs 'age of onset 15-17' or between 'occasional use' vs 'non-users'

Horwood 2012
    Strengths:
    - Pooled data from four longitudinal studies in Australia and New Zealand - CHDS, VAHCS, the Australian Temperament Project, and the Personality and Total Health Study, with almost 7000 total subjects

- Four categories for frequency of marijuana use were used: none, less than monthly, monthly and weekly
- Depression scales were standardized to a mean of 100 and SD of 10, to allow for combination
- Fixed effects regression was used to control for confounding, since the studies had assessed different potential confounding variables
- Analysis of reciprocal relationships showed that depression did not have a significant effect on marijuana use, while marijuana use did have a significant effect on depression

Minor limitations:
- Ages ranged up to 34 in one of the studies, and 30 in another, but marijuana use was predominantly during adolescence and early 20's
- Depressive symptoms were evaluated using several different methods across studies, and the standardization assumes an interval relationship of scores, which might not be accurate

Huas 2008

Strengths:
- 18,500 subjects from grades 6-12 in France
- 89% participation rate
- Marijuana use categories were never use, past use (at least once), occasional use and regular use
- 8.3% were occasional users and 8.0% regular users
- Adjusted for age, gender, alcohol and tobacco use
- p-values for listed findings were all <0.01 or smaller

Major limitations:
- Cross-sectional study where marijuana use categories were based on use during the last month, while outcomes were measured during the last 12 months or lifetime

Minor limitations:
- Actual outcome event rates were not given, though they can be assumed adequate in such a large sample
- 'Former users' included any lifetime use, and 'occasional users' included any use in the last 30 days
- Did not adjust for family, social or personal factors found by other studies to be related to the other variables

Jessor 1980

Strengths:
- Component of the National Longitudinal Study of Adolescent Health
- Stratified random sample provided adolescents in grades 7-12 throughout the United States
- 10,405 subjects completed sufficient questions for analysis in this study
- The study illustrates marijuana use as part of a 'syndrome' of adolescent behavior, and it was not intended to specifically demonstrate effects of marijuana

Minor limitations:
- Marijuana use was assessed using levels of 'involvement': "Have you tried marijuana?", "Have you been high or stoned on marijuana?", "Do you or someone close to you keep marijuana available?", "Do you use marijuana twice a week or more?"
- Variables were analyzed individually relative to marijuana use, without adjustment

Kokkevi 2012
Strengths:
- 45,086 students from sixteen European countries
- All were born in 1991, and 15-16 years old at the time of the study
- Adjusted for gender country, tobacco use, alcohol use, nonprescription use of prescription medication and other illegal drug use
Major limitations:
- Cross-sectional study with marijuana use defined as any use in the last 30 days, while suicide attempt was 'ever'

Kuepper 2011
Strengths:
- Longitudinal study of 1923 subjects age 14-24 years, randomly selected in Munich from the population registry
- Psychotic symptoms were new between a 3-year follow-up and an 8-year follow-up, analyzed relative to marijuana use prior to the 3-year follow-up
- Adjusted for age, gender, SES, use of other drugs, childhood trauma, urban/rural, and psychiatric disorder at baseline
- Sensitivity analysis confirmed results with imputed data
Minor limitations:
- Marijuana use was simply 5 or more times
- Definition of psychotic symptoms was 'yes' to any psychosis item on the CIDI
- Not adjusted for psychosis at baseline, or for tobacco or alcohol

Lynne-Landsman 2010
Strengths:
- Longitudinal study from 1st grade to age 21
- 678 subjects in Baltimore, MD
- Those classified in one of the two marijuana user groups had used at least 10 times during high school
Major limitations:
- Complex modeling was done, but associations between marijuana use and later outcomes appears to be presented without adjustment
Minor limitations:
- Urban African American youth only
- 75% of subjects still involved to the end of the study
- The two categories of marijuana users were not easily defined

Medina 2007
    Strengths:
- 31 users and 34 controls among 16-18 year olds in southern California
- Marijuana users had to have at least 60 lifetime uses of marijuana, plus recent use at the start of the study
- 28 day abstinence confirmed with regular testing
- Excluded psychiatric disorders, psycho-active medication use, chronic illness or neurological condition, head trauma, prenatal alcohol or drug exposure, premature birth or complicated delivery, learning disability or delay
- Controlled for depressive symptoms and alcohol use
- Bonferroni correction was used for multiple comparisons

    Minor limitations:
- The marijuana users group had some previous use of other drugs

Meier 2012
    Strengths:
- Longitudinal study of a birth cohort with 1037 subjects in Dunedin, New Zealand
- Within-person change studied

    Minor limitations:
- Marijuana use was measured starting at age 18, not younger
- Use was defined as meeting DSM criteria for dependence
- Actual effect size is not given for the analysis adjusting for acute marijuana intoxication, tobacco, alcohol or hard-drug dependence, and schizophrenia
- Adjustment for completing HS is shown individually, but not included in the full model
- Many analyzed subgroups were small (12-20 subjects)
- The reported decline of 8 IQ points is based only on 23 subjects meeting criteria for marijuana dependence at three (or more) different time points, beginning at age 18. This is not a very relevant population to adolescent users overall.

Miettunen 2013
    Strengths:
- Longitudinal birth cohort study in Finland with time-points at 8 yrs old, 15-16 and 20-25
- 6349 subjects in the final analysis
- Age 8 internalizing problems (emotional/psychiatric) and externalizing problems (behavioral) were based on teacher and parent surveys
- Cases of depression or anxiety requiring hospital treatment were available from the national discharge register for everyone living in Finland (no missing or self-report data)
- Adjusted for place of residence, family pattern, social status, parental alcohol use, parental psychiatric disorders, and externalizing or internalizing problems at age 8 or 15-16

Minor limitations:
- 78% of 8 yr olds evaluated took part at 15-16 yrs old, however attrition analysis did not identify differences based on non-participants
- Marijuana use was lifetime ever or never
- Lower marijuana use (5-6%) than U.S. rates
- Wide CI for lack of effect in boys (OR 2.2, CI 0.6-7.9)

Moss 2014
Strengths:
- Longitudinal study starting with adolescents in grades 7-12, and looking at substance use 14 years later
- 15,701 subjects in the National Longitudinal Study of Adolescent Health in the United States
- Separated and compared categories of use among 7-12th graders as marijuana only, alcohol only, tobacco only, and combinations of the three (plus those who didn't use any of the three), with 137 in the smallest group
- Adjusted for age, gender, and race/ethnicity

Minor limitations:
- Not adjusted for many family, social or personal factors that other studies have found related to substance use
- Use was not quantified, it was simply use or no use
- Specific confidence intervals or p-values were not given for comparisons, just reporting that p<0.05

Nakawaki 2012
Strengths:
- Used pooled data from 7 years of the National Survey on Drug Use and Health, a broad U.S. focused survey
- Included 126,764 adolescents age 12-17 surveyed from 2003-2009
- Adjusted for gender, age, family income, race, parental status, populations density, tobacco and alcohol use
- Questions included age at first use for each substance, allowing a temporal relationship to be measured
- Used multinomial logistic regression

Minor Limitations:
- Cross-sectional study
- 8-9% of the 12-17 year olds surveyed had missing data and were omitted from analysis
- Did not distinguish by amount of use for any substance

Pahl 2011
Strengths:
- Longitudinal study with five time-points from 7-10th grade through 19 years later
- 474 females from East Harlem, NY

- Adjusted for age, race/ethnicity, teen deviance/risk taking, teen level of conflict with mother, teen depression, teen anger/hostility, and adult household income and education
- Depression and anger/hostility were measured with the Hopkins Symptom Checklist, a validated instrument - the depression portion correlates well with DSM diagnosis

Minor limitations:
- African American and Puerto Rican women only
- Marijuana use was defined by 3 'trajectories' - those who used as adolescents and continued use through their 20's, those who used as adolescents and quit, and nonusers
- All participants were in their 20's by the third time-point, so much of the marijuana use is beyond adolescence
- Depression and anger/hostility were not measured until age 32

Pope 2003
Strengths:
- Longitudinal study following through 28 days of abstinence
- Demographically diverse
- 209 subjects included current, former and non-using adult groups, divided by marijuana use onset at age 16 or younger vs. at age 17 or older
- Users had used at least 5000 times lifetime
- 'Non-users' had to have used at least once, to reduce residual confounders
- Excluded other drug use, alcohol abuse, psychiatric disorders or medications, past head injury or other condition that may affect cognitive function
- 28 day abstinence confirmed with frequent urine tests
- Adjusted for age, gender, ethnicity, parental education, 1st degree relative substance abuse, and 1st degree relative psychiatric disorder
- Secondary analysis adjusted for features of ADHD or conduct disorder
- Confirmatory analysis was done with definitions of early onset at age 15 or less, and age 14 or less, with consistent results
- Comparisons were all planned in advance, but because multiple tests were used, alpha was set at 0.01

Minor limitations:
- Analysis done with adjustment for verbal IQ score no longer showed significant differences, however, IQ was inversely related to lifetime episodes of marijuana use, and so may have been a mediator between marijuana use and test performance rather than a confounder
- Did not separately analyze those who were using regularly before the study from those who had quit, though all subjects had 28+ days abstinence at the time of testing

Rasic 2013

    Strengths:
- Longitudinal study of 1582 students at two time-points (grade 10 and grade 12) in northern Nova Scotia
- Depression assessed with the Center for Epidemiologic Studies Depression Scale, a validated instrument correlated with DSM-IV diagnostic criteria
- Suicide ideation and attempt assessed with questions from the CDC's Youth Risk Behavior Surveillance System survey
- Secondary analysis used four levels of marijuana use, roughly no use, occasional (1-2 times/month), regular (3-9 times/month) and regular/heavy (10+ times/month)
- Adjusted for age, gender, school grades, living situation, and alcohol use
- Risk for suicide ideation or attempt had tight CIs (0.94-1.07 & 0.98-1.09)

    Minor limitations:
- 61.9% of initial participants were present for the follow-up, with many lost due to absence on the day of the survey or dropping out of school
- Depression risk was a small effect with CI close to 1 (OR 1.1, CI 1.01-1.19), and the dose effect is slight (OR's 1.02, 1.10, 1.16)

Schepsis 2008

    Strengths:
- Used data from the 2005 National Survey on Drug Use and Health, a broad U.S. focused survey
- 18,678 adolescents age 12-17
- Two measures were evaluated - any misuse (non-prescription use) of prescription drugs, and presence of one or more symptoms of prescription drug abuse or dependence
- Adjusted for age, gender, race, moved in the past year, parents in household, school grades, past criminal confinement, risk taking, past mental health treatment, past major depressive episode, alcohol, tobacco, inhalants and cocaine
- Univariate regression followed by multivariate to distinguish risk due to different variables
- Weighted for population based rates of variables to reduce sampling bias
- Sizeable outcome, with 8.2% of adolescents misusing prescription medications and 3.0% having one or more symptoms of abuse or dependence in the past year

    Minor limitations:
- Cross-sectional study with both outcome and predictor variables measured for the past year - no temporal relationship
- 76% of 12-17 year olds surveyed gave full interview responses, missing data were imputed
- Marijuana use was simply use or no use in the prior year

Spears 2014
　　Strengths
- Longitudinal study with evaluation at baseline and 6-months later
- 2042 students in 10th grade in Santiago, Chile
- Sensitivity analysis showed minimal difference with imputed data compared with gathered data, so analysis was done without imputation
- Adjusted for age, gender, depression, anxiety, school connectedness, problem solving skill, suicidal thoughts, alcohol, tobacco, and trial arm

　　Minor limitations:
- Marijuana use was 'never' vs 'at least once'
- Analyzed only self-harm as an outcome, not suicide ideation or attempt
- Self-harm due to suicide ideation or attempt, and its association with marijuana use, would be masked by adjusting for suicide ideation and depression
- Done as a nested study within a randomized trial of school-based intervention to reduce depression, adjusted for trial arm, but still likely to cause different behavior and associations within the study population
- Wide CI (OR 1.46, CI 0.85-2.51)

Swift 2008
　　Strengths:
- Longitudinal study over 10 years, with 8 time-points
- Sample selected by cluster randomization from all schools in Victoria, Australia
- 1943 subjects starting in 9th grade
- 98% of adolescents in Victoria who should be attending school in 9th grade were, and thus were potential subjects
- Marijuana use categories were none, occasional, regular or heavy
- Early initiation defined as starting before 11th grade
- Dependence was defined at time-point 8 according to DSM-IV criteria
- Adjusted for sex, urban/rural, cigarette smoking, alcohol use, depression/anxiety, antisocial behavior, parental divorce, parental cigarette use and parental HS completion
- Large numbers of subjects in each risk level and outcome led to good confidence intervals

　　Minor limitations:
- 22% of the initial participants were not interviewed at the final time-point, including 14% who refused and 8% with lost contact
- 36% of subjects missed at least one time-point, and missing data was imputed
- Though randomly selected, the cluster method could have resulted in subject groups that are different from the general population

Swift 2012
   Strengths:
   - Same as Swift 2008
   - Less than 2% loss between time-points 8 and 9
   - Tobacco, amphetamine, cocaine, ecstasy and high-risk alcohol use were each analyzed separately
   - High-risk alcohol use was defined as more than 14 standard drinks in the past week
   - Still had large numbers of subjects in each risk level and outcome, leading to good confidence intervals
   Minor limitations:
   - Same as Swift 2008
   - Amphetamine, cocaine and ecstasy use were defined simply as any use in the past year
   - Cigarette use was defined simply as any use in the past month
   - Analyzed time-points were marijuana use at 20 compared with other substances at 24, and marijuana use at 24 compared with other substances at 29, and these were combined into a single analysis

van Os 2002
   Strengths:
   - Longitudinal study, part of the Netherlands Mental Health Survey and Incidence Study, with 4045 subjects in final analysis
   - Multistage, stratified, random sampling
   - Only individuals with no psychosis symptoms at baseline were included
   - Adjusted for age, gender, ethnicity, education, employment, marital status, urbanicity, and experience with discrimination
   - Multiple regression models separated the effect of use at baseline from use at later assessment points, and the effect for marijuana use from the effect of other drugs, and baseline marijuana use still had the strongest association with the outcomes
   Minor limitations:
   - Only 57% of initial cohort had sufficient data for final analysis - sensitivity analysis showed wide potential variation in results
   - Incident psychosis was measured only three years after baseline
   - Mean age was 41 years old, and eligibility included ages 18-64
   - Did not adjust for tobacco or alcohol use

Wang 2013
   Strengths:
   - Ecological (retrospective) study based on ICD-9 coding for the busiest pediatric hospital emergency department in Colorado
   - Compared multi-year periods before and after expansion of medical marijuana sales in the state
   - 790 and 588 unintentional ingestions (of any substance) were reviewed in the two periods studied

- Marijuana exposure confirmed by urine toxicology

Minor limitations:
- A single medical record reviewer was not blind to group, however an objective measure (urine toxicology) was the primary criteria used
- Hospital practices, including urine testing for marijuana, may have been different between the two periods

Wang 2014

Strengths:
- Ecological (retrospective) study using US national level data from the American Association of Poison Control Centers Data, over a 7 year period
- Only single-substance exposures were studied
- States level comparisons, grouped by marijuana legalization before 2005, from 2005 to 2011, and no legalization

Minor limitations:
- Exposures were not necessarily confirmed with biologic testing
- Poison center practices between states might be different, for example, sensitivity to marijuana exposure in marijuana legalized states might be higher

Zammit 2002

Strengths:
- Longitudinal study of over 50,000 Swedish conscripts
- Includes over 97% of the male population 18-20 years old at the start of the study
- Total marijuana use prior to study start was assessed, and analyzed both as any use and categorically by amount
- Schizophrenia was based on the Swedish national hospital discharge register over the next 25 years - nearly all cases of schizophrenia should have been ascertained with this method
- Adjusted for psychiatric diagnoses at study start, IQ score, tobacco or alcohol use, other drug use, disturbed childhood behavior, social integration, family history of psychiatric illness, place of upbringing, paternal age, family financial situation, and father's occupation
- Results were analyzed excluding individuals diagnosed with schizophrenia within 5 years of baseline, and significant effect remained for those who had used 11 times or more

Minor limitations:
- Males only
- Questionnaires were non-anonymous

REFRENCES CITED

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: examination of the evidence. Br J Psychiatry, 184, 110-117.

Becker, M. P., Collins, P. F., & Luciana, M. (2014). Neurocognition in college-aged daily marijuana users. J Clin Exp Neuropsychol, 36(4), 379-398. doi: 10.1080/13803395.2014.893996

Block, R. I., Farnham, S., Braverman, K., Noyes Jr, R., & Ghoneim, M. M. (1990). Long-term marijuana use and subsequent effects on learning and cognitive functions related to school achievement: Preliminary study. NIDA Research Monograph Series(101), 96-111.

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., & Cadet, J. L. (2002). Dose-related neurocognitive effects of marijuana use. Neurology, 59(9), 1337-1343.

Brook, J. S., Balka, E. B., & Whiteman, M. (1999). The risks for late adolescence of early adolescent marijuana use. Am J Public Health, 89(10), 1549-1554.

Burns, J. K. (2013). Pathways from Cannabis to Psychosis: A Review of the Evidence. Front Psychiatry, 4, 128. doi: 10.3389/fpsyt.2013.00128

Castle, D. J. (2013). Cannabis and psychosis: what causes what? F1000 Med Rep, 5,1.doi: 10.3410/m5-1

Chadwick, B., Miller, M. L., & Hurd, Y. L. (2013). Cannabis Use during Adolescent Development: Susceptibility to Psychiatric Illness. Front Psychiatry, 4, 129. doi: 10.3389/fpsyt.2013.00129

Consoli, A., Peyre, H., Speranza, M., Hassler, C., Falissard, B., Touchette, E., . . . Révah-Lévy, A. (2013). Suicidal behaviors in depressed adolescents: role of perceived relationships in the family. Child Adolesc Psychiatry Ment Health, 7(1), 8. doi: 10.1186/1753-2000-7-8

Crome, I., & Bloor, R. (2005). Substance misuse and psychiatric comorbidity in adolescents. Curr Opin Psychiatry, 18(4), 435-439. doi: 10.1097/01.yco.0000172064.86272.8e

Degenhardt, L., Coffey, C., Romaniuk, H., Swift, W., Carlin, J. B., Hall, W. D., & Patton, G. C. (2013). The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. Addiction, 108(1), 124-133. doi: 10.1111/j.1360-0443.2012.04015.x

Fergusson, D. M., & Boden, J. M. (2008). Cannabis use and later life outcomes. Addiction, 103(6), 969-976; discussion 977-968. doi: 10.1111/j.1360-0443.2008.02221.x

Fergusson, D. M., & Horwood, L. J. (2000). Does cannabis use encourage other forms of illicit drug use? Addiction, 95(4), 505-520.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2006). Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. Addiction, 101(4), 556-569. doi: 10.1111/j.1360-0443.2005.01322.x

Fergusson, D. M., Horwood, L. J., & Beautrais, A. L. (2003). Cannabis and educational achievement. Addiction, 98(12), 1681-1692.

Fergusson, D. M., Horwood, L. J., & Ridder, E. M. (2005). Tests of causal linkages between cannabis use and psychotic symptoms. Addiction, 100(3), 354-366. doi: 10.1111/j.1360-0443.2005.01001.x

Fiellin, L. E., Tetrault, J. M., Becker, W. C., Fiellin, D. A., & Hoff, R. A. (2013). Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. J Adolesc Health, 52(2), 158-163. doi: 10.1016/j.jadohealth.2012.06.010

Fried, P. A., Watkinson, B., & Gray, R. (2005). Neurocognitive consequences of marihuana--a comparison with pre-drug performance. Neurotoxicol Teratol, 27(2), 231-239. doi: 10.1016/j.ntt.2004.11.003

Fried, P., Watkinson, B., James, D., & Gray, R. (2002). Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults.Cmaj, 166(7), 887-891.

Hall, W. (2009). The adverse health effects of cannabis use: what are they, and what are their implications for policy? Int J Drug Policy, 20(6), 458-466. doi: 10.1016/j.drugpo.2009.02.013

Hall, W., & Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. Drug Test Anal, 6(1-2), 39-45. doi: 10.1002/dta.1506

Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U., & van Os, J. (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. Bmj, 330(7481), 11. doi: 10.1136/bmj.38267.664086.63

Hooper, S. R., Woolley, D., & De Bellis, M. D. (2014). Intellectual, neurocognitive, and academic achievement in abstinent adolescents with cannabis use disorder.Psychopharmacology (Berl), 231(8), 1467-1477. doi: 10.1007/s00213-014-3463-z

Horwood, L. J., Fergusson, D. M., Coffey, C., Patton, G. C., Tait, R., Smart, D., . . . Hutchinson, D. M. (2012). Cannabis and depression: an integrative data analysis of four Australasian cohorts. Drug Alcohol Depend, 126(3), 369-378. doi: 10.1016/j.drugalcdep.2012.06.002

Horwood, L. J., Fergusson, D. M., Hayatbakhsh, M. R., Najman, J. M., Coffey, C., Patton, G. C., . . . Hutchinson, D. M. (2010). Cannabis use and educational achievement: findings from three Australasian cohort studies. Drug Alcohol Depend, 110(3), 247-253. doi: 10.1016/j.drugalcdep.2010.03.008

Huas, C., Hassler, C., & Choquet, M. (2008). Has occasional cannabis use among adolescents also to be considered as a risk marker? Eur J Public Health, 18(6), 626-629. doi: 10.1093/eurpub/ckn065

Jessor, R., Chase, J. A., & Donovan, J. E. (1980). Psychosocial correlates of marijuana use and problem drinking in a national sample of adolescents. Am J Public Health, 70(6), 604-613.

Kokkevi, A., Richardson, C., Olszewski, D., Matias, J., Monshouwer, K., & Bjarnason, T. (2012). Multiple substance use and self-reported suicide attempts by adolescents in 16 European countries. Eur Child Adolesc Psychiatry, 21(8), 443-450. doi: 10.1007/s00787-012-0276-7

Kuepper, R., van Os, J., Lieb, R., Wittchen, H. U., Hofler, M., & Henquet, C. (2011). Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. Bmj, 342, d738. doi: 10.1136/bmj.d738

Lisdahl, K. M., Gilbart, E. R., Wright, N. E., & Shollenbarger, S. (2013). Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. Front Psychiatry, 4, 53. doi: 10.3389/fpsyt.2013.00053

Lynne-Landsman, S. D., Bradshaw, C. P., & Ialongo, N. S. (2010). Testing a developmental cascade model of adolescent substance use trajectories and young adult adjustment. Dev Psychopathol, 22(4), 933-948. doi: 10.1017/S0954579410000556

Medina, K. L., Hanson, K. L., Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J., & Tapert, S. F. (2007). Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. J Int Neuropsychol Soc, 13(5), 807-820. doi: 10.1017/s1355617707071032

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S., . . . Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. Proc Natl Acad Sci U S A, 109(40), E2657-2664. doi: 10.1073/pnas.1206820109

Miettunen, J., Murray, G. K., Jones, P. B., Mäki, P., Ebeling, H., Taanila, A., . . . Moilanen, I. (2013). Longitudinal associations between childhood and adulthood externalizing andinternalizing psychopathology and adolescent substance use. Psychol Med, 1-12. doi: 10.1017/S0033291713002328

Moss, H. B., Chen, C. M., & Yi, H. Y. (2014). Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample. Drug Alcohol Depend, 136, 51-62. doi: 10.1016/j.drugalcdep.2013.12.011

Nakawaki, B., & Crano, W. D. (2012). Predicting adolescents' persistence, non-persistence, and recent onset of nonmedical use of opioids and stimulants. Addict Behav, 37(6), 716-721. doi: 10.1016/j.addbeh.2012.02.011

Pahl, K., Brook, J. S., & Koppel, J. (2011). Trajectories of marijuana use and psychological adjustment among urban African American and Puerto Rican women. Psychol Med, 41(8), 1775-1783. doi: 10.1017/S0033291710002345

Parakh, P., & Basu, D. (2013). Cannabis and psychosis: have we found the missing links? Asian J Psychiatr, 6(4), 281-287. doi: 10.1016/j.ajp.2013.03.012

Pattij, T., Wiskerke, J., & Schoffelmeer, A. N. (2008). Cannabinoid modulation of executive functions. Eur J Pharmacol, 585(2-3), 458-463. doi: 10.1016/j.ejphar.2008.02.099

Pope, H. G., Jr., Gruber, A. J., Hudson, J. I., Cohane, G., Huestis, M. A., & Yurgelun-Todd, D. (2003). Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend, 69(3), 303-310.

Radhakrishnan, R., Wilkinson, S. T., & D'Souza, D. C. (2014). Gone to Pot - A Review of the Association between Cannabis and Psychosis. Front Psychiatry, 5, 54. doi: 10.3389/fpsyt.2014.00054

Rasic, D., Weerasinghe, S., Asbridge, M., & Langille, D. B. (2013). Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. Drug Alcohol Depend, 129(1-2), 49-53. doi: 10.1016/j.drugalcdep.2012.09.009

Schepis, T. S., & Krishnan-Sarin, S. (2008). Characterizing adolescent prescription misusers: a population-based study. J Am Acad Child Adolesc Psychiatry, 47(7), 745-754. doi: 10.1097/CHI.0b013e318172ef0ld

Schweinsburg, A. D., Brown, S. A., & Tapert, S. F. (2008). The influence of marijuana use on neurocognitive functioning in adolescents. Curr Drug Abuse Rev, 1(1), 99-111.

Serafini, G., Pompili, M., Innamorati, M., Temple, E. C., Amore, M., Borgwardt, S., & Girardi, P. (2013). The Association between Cannabis Use, Mental Illness, and Suicidal Behavior: What is the Role of Hopelessness? Front Psychiatry, 4, 125. doi: 10.3389/fpsyt.2013.00125

Shapiro, G. K., & Buckley-Hunter, L. (2010). What every adolescent needs to know: cannabis can cause psychosis. J Psychosom Res, 69(6), 533-539. doi: 10.1016/j.jpsychores.2010.04.002

Spears, M., Montgomery, A. A., Gunnell, D., & Araya, R. (2014). Factors associated with the development of self-harm amongst a socio-economically deprived cohort of adolescents in Santiago, Chile. Soc Psychiatry Psychiatr Epidemiol, 49(4), 629-637. doi: 10.1007/s00127-013-0767-y

Swift, W., Coffey, C., Carlin, J. B., Degenhardt, L., & Patton, G. C. (2008). Adolescentcannabis users at 24 years: trajectories to regular weekly use and dependence in young adulthood. Addiction, 103(8), 1361-1370. doi: 10.1111/j.1360-0443.2008.02246.x

Swift, W., Coffey, C., Degenhardt, L., Carlin, J. B., Romaniuk, H., & Patton, G. C. (2012). Cannabis and progression to other substance use in young adults: findings from a 13-year prospective population-based study. J Epidemiol Community Health, 66(7), e26. doi: 10.1136/jech.2010.129056

Trezza, V., Cuomo, V., & Vanderschuren, L. J. (2008). Cannabis and the developing brain: insights from behavior. Eur J Pharmacol, 585(2-3), 441-452. doi: 10.1016/j.ejphar.2008.01.058

van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol, 156(4), 319-327.

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. (2014). Adverse health effects of marijuana use. N Engl J Med, 370(23), 2219-2227. doi: 10.1056/NEJMra1402309

Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. Bmj, 325(7374), 1199.

Marijuana Dose and Drug Interactions

Evidence Summary

Marijuana Dose and Drug Interactions: Research Questions and Findings

Prepared for the Colorado Department of Public Health and the Environment
Retail Marijuana Public Health Advisory Committee

by

Kimberly Siegel, MD, MPH

November 2014

DEFINITIONS, BACKGROUND AND GENERAL REMARKS

- The term "marijuana cigarette" is synonymous with "joint."

- THC = delta 9-tetrahydrocannabinol

- A typical "currently available" marijuana cigarette is herein defined to have a weight of approximately 0.5 gram and a THC content of 12-23%.(1) Therefore, a typical joint contains 60-115 mg THC. However, in the community, size and THC content of marijuana cigarettes varies tremendously (7 to > 30% THC).

  - <u>High and variable potency of marijuana cigarettes in Colorado may have important implications for the applicability of our findings to Colorado's population.</u>

- A smoked dose = total amount of THC (in mg) in a cigarette = (weight of cigarette) x (percent THC content).

- An oral dose = total amount (in mg) of ingested THC.

- The standard serving size of a marijuana edible in Colorado is 10 mg THC.

- THC is primarily measured in whole blood, serum, or plasma. Serum and plasma THC concentrations reported in studies have been converted to whole blood THC concentrations in this document, except in figures copied from the original articles, to facilitate comparisons. Whole blood THC concentration = (0.5) x (plasma or serum THC concentration).(2, 3)

- Heavy marijuana user: daily or near daily use ($\geq$ 4 days per week) for at least the past 6 months.

- Moderate user: use > once per week but < 4 days per week.

- Occasional marijuana user: $\leq$ weekly use.

- Recent survey data on quantity of marijuana used by Coloradans shows that daily (heavy) users use about 1.7 grams on the days they use, moderate users use about 0.7 grams, and occasional users use about 0.4 to 0.7 grams.(4)

Table 1. Results from the Colorado Marijuana Use Survey (from Light et al.)(4)

Reported Frequency of Cannabis Usage	Share of Responses	Frequency on Days of Cannabis Use	Typical Dried Bud Consumption Per Day (Grams)[2]	Adjusted Dried Bud Consumption Per Day (Grams)[1]
Daily	51.1%	3.29	1.41	1.71
2-3 Times a Week	16.5%	1.69	0.53	0.65
Once a Week	4.5%	1.73	0.65	0.64
2-3 Times a Month	5.7%	1.37	0.44	0.43
Once a Month	2.4%	1.38	0.38	0.49
Less than Once a Month	9.0%	1.13	0.85	0.70
Never	0.9%	-	-	-

Unweighted; n=299; [1]5 or more recoded as "5." See: "Marijuana Use Survey", May 2014, submitted to the Colorado Department of Revenue.

- Important pharmacokinetic and pharmacodynamics features: There are many characteristics of marijuana and its users that influence systemic dose and dose-response.
  a. General:
      i. Potency (THC content) of the marijuana plant material.(5)
      ii. The relative THC and cannabidiol (and other cannabinoids) content of the marijuana.(2)
      iii. Prior exposure to and experience with marijuana.(5)
      iv. Tolerance(5, 6)
      v. Genetic differences in cannabinoid receptor structure and function.(5)
      vi. Genetic differences in cannabinoid metabolism: Homozygosity for CYP2C9*3 allele appears to impair THC metabolism, causing greater intoxication.(5)
      vii. Changes to cannabinoid receptor distribution, density or function due to medical problems.(5)
      viii. Hysteresis: Definition: "the retardation or lagging of an effect behind the cause of the effect"(7)
          1. There is delay in onset of effects compared to blood/plasma THC levels.(5, 8)
          2. Blood/plasma THC concentrations begin to decrease before the point of peak effects even though effects appear rapidly after smoking begins.(2)
          3. Blood/plasma THC levels decrease faster than effects. (8-10)
          4. THC hysteresis may result in impairment lasting longer than elevated THC blood concentrations.
  b. For smoking
      i. Bioavailability is greater and onset of effects is faster with smoking and vaporization compared to oral ingestion.(2)

      ii. Smoking topography (depth, volume, frequency and duration of inhalation) and titration of dose.(2, 6, 11)
           1. Subjects tend to titrate their smoked doses up or down through alteration of their smoking topography, depending on the potency of the cigarettes.(6, 11, 12)
     iii. There is wide inter-individual variability in blood/plasma/serum THC concentrations for similar smoked doses, even with paced smoking protocols.(13) See **Figure 1** in the Appendix.

c. For ingestion
       i. Bioavailability is less and onset of effects is slower with ingestion compared to smoking or vaporization.(2)
      ii. The is wide inter-individual variability in blood/plasma/serum THC concentrations after ingestion of the same dose due to differences in degradation in the stomach, GI absorption and first-pass metabolism.(2, 14) See **Figure 2** in the Appendix.
           1. Full vs. empty stomach: Dronabinol trials were done in a fasting state. Dronabinol dosing instructions for AIDS-related anorexia are to take doses before meals. For chemotherapy-induced nausea, instructions are to take 1-3 hrs before chemotherapy session.(15)
           2. Perez-Reyes et al reported that rates and amounts of THC absorption varied considerably among individuals who had received it in the same oral vehicle. The authors noted that experience with the same individuals in multiple experiments suggested that good absorbers always absorbed well and poor absorbers always absorbed poorly.(13)
     iii. Substrate – Perez-Reyes et al measured plasma radioactivity levels after ingestion of tritium-labeled THC in different substrates. Mean plasma radioactivity increased fastest and to the highest peak when sodium glycocholate (a bile acid composed of glycine conjugated to cholic acid) was the vehicle.(14) The next highest mean peak level occurred with sesame oil, followed, in descending order, by Tween-80 (a hydrophilic emulsifier)(16), ethanol, and the combination sodium glycocholate-ethanol. For all, peak plasma radioactivity levels occurred at 2-3 hrs post-ingestion.

d. For vaporization
       i. Vaporization temperature: Higher levels of cannabinoids are released at higher temperatures.(5)

METHODS

- This literature review addressed the pharmacokinetics and acute effects of marijuana (THC)in occasional and/or naïve users, NOT heavy users, except where specifically stated otherwise. Tolerance to acute effects in heavy users has been clearly demonstrated, but uncertainty exists regarding the extent to which tolerance mitigates impairment in highly complex tasks or safety sensitive tasks such as driving.(8, 17-21)

- Method for identification of drugs with potential interaction with marijuana.
  - Review of dronabinol and cannabis drug monographs from the manufacturer (Marinol) and in Lexi-Comp and Micromedex online drug databases.
  - Identification of drugs that are substrates or inhibitors of the cytochrome P450 enzymes that metabolize THC: 2C9, 2C19, and 3A4.
    - PubMed searches for primary literature about interactions of each drug with marijuana and/or interaction searches using online drug databases (Lexi-Comp and Micromedix) for these drugs with marijuana and dronabinol.

- No animal studies were reviewed because adequate human studies are available, and/or animal studies are not applicable to the research questions addressed .

RESEARCH QUESTIONS, FINDINGS, AND EVIDENCE STATEMENTS

Research questions are in *italics.*

Evidence statements are in **bold.**

1. *It is well established that whole blood, plasma, or serum THC concentration, not urine or oral fluid cannabinoids, is the most accurate biologic test for marijuana-induced impairment in occasional or naïve users.(21) However, determining a blood/plasma/serum cutoff level for impairment, mainly with respect to driving, has been more difficult. What evidence supports Colorado's 5 ng/mL whole blood THC limit for unimpaired driving? (1 evidence statement)*

a. **EVIDENCE STATEMENT 1: We found substantial evidence for meaningful driving impairment in occasional users with whole blood THC of 2-5 ng/mL.**
   i. Evidence summary
      1. 3 high quality findings from 2 meta-analyses (Berghaus 2011, Berghaus 1995)
      2. 1 high quality finding from a systematic review (Hartman & Huestis 2013)
      3. 1 medium quality finding from a non-systematic review (Grotenhermen 2007)
   ii. Evidence details: The evidence supporting this statement is drawn from meta-analyses and reviews of many experimental studies and a few epidemiologic studies, as summarized in **Table 2**.

Table 2. Systematic reviews and meta-analyses addressing blood THC levels associated with driving impairment.

Non-Systematic Review (NR), Systematic Review (SR), or Meta-analysis (M)	Number of Studies	Whole Blood THC Level (ng/mL) Associated with Significant Impairment
Berghaus et al (2011)(M)(22)	Smoked: 78 experimental studies* (888 effects) Oral: 21 experimental studies* (482 effects)	Smoked: 1.9 (range 1.7-2.3) equivalent to BAC 0.05% Oral: 1.9 (range 1.6-2.3) equivalent to BAC 0.05%
Berghaus et al (1995)(M)(23)	60 experimental studies	3-5.5
Grotenhermen et al (2007)(NR)(3)	4 epidemiologic, about 3 experimental studies, including Berghaus meta-analysis (1995)	3.5-5
Hartman & Huestis (2013)(SR)(21)	17 experimental, 5 epidemiologic	2-5

BAC = blood alcohol concentration.   * Published after 1993

b. Berghaus et al (2011) found in a meta-analysis of 78 experimental smoking studies and 21 experimental oral THC studies (all published after 1993) that mean whole blood THC of 1.9 ng/mL (rang 1.6-2.3) was associated with a level of driving impairment equivalent to BAC 0.05%.(22)

c. Berghaus et al (1995) performed a meta-analysis of 60 experimental studies of smoked marijuana and driving skills and found that 50% of cumulated performance results showed significant decrements at 3 ng/mL whole blood

THC for tracking, 4 ng/mL for psychomotor skills, 4.5 ng/mL for attention, 5.5 ng/mL for divided attention and 5.5 ng/mL for all performance areas taken together.(23)

d. Grotenhermen et al (2007) reported the conclusion of an international working group of experts, after non-systematic evaluation of experimental and epidemiological evidence, that whole blood THC 3.5-5 ng/mL was the most suitable range for a per se limit for driving impairment based in part on experimental human studies and comparison to a BAC of 0.05%.(3)

e. In their recent systematic review, Hartman and Huestis (2013) reported that whole blood levels of 2-5 ng/mL and driving within 1 hour of marijuana use are associated with substantial driving impairment in occasional users.(21)

2. *What dose produces a whole blood level of 5 ng/mL, and/or impairment?*
   (5 evidence statements)

   a. By smoking:
      i. **EVIDENCE STATEMENT 2: We found substantial evidence that smoking more than about 10 mg THC (or part of a currently available marijuana cigarette) is likely to yield whole blood THC concentrations near or above 5 ng/mL within 10 minutes.**
         1. Evidence summary
            a. A high quality finding from an analysis of pooled data from 5 pharmacokinetic studies (Berghaus 2011)(22)
            b. 3 high quality findings from original pharmacokinetic studies (Huestis 1992, Ramaekers 2006, Reeve 1983)(13, 24, 25)
            c. No opposing findings
         2. Evidence details
            a. Berghaus et al (2011) in an analysis of pooled data from 5 pharmacokinetic studies (n = 36 observations) reported a peak whole blood THC concentration of 44 ng/mL a mean of 7 minutes after smoking 15 mg THC.(22)
            b. Huestis et al (1992) demonstrated that a single inhalation of a 1.75% or 3.55% THC cigarette (cigarette weight not specified) produced immediate (within 12 minutes) mean whole blood THC concentrations of 3.5 and 9.1 ng/mL, respectively).(13) There was wide inter-individual variation in THC levels despite use of a paced smoking protocol. See **Figures 1** and **3** in the Appendix.
            c. Ramaekers et al measured whole blood THC levels of 29 ng/mL and 47.6 ng/mL five minutes after smoking 250

mcg/kg (17.5 mg/70 kg) and 500 mcg/kg (35 mg/70 kg), respectively.(24)

d. Reeve et al measured whole blood THC levels of 0-66 ng/mL five minutes after 19 subjects (infrequent marijuana users) smoked whatever portion of an 18 mg THC cigarette produced a reasonable subjective high.(25) Mean whole blood THC level at 5 minutes post-smoking was 22.1 ng/mL. Two subjects had 2.5 and 3.5 ng/mL THC levels at baseline (before smoking).

ii. **EVIDENCE STATEMENT 3: We found substantial evidence that, for occasional users, smoking more than about 10 mg THC (or part of a currently available marijuana cigarette) is likely to meaningfully impair driving ability.**

1. Evidence summary
   a. 2 high quality findings from meta-analyses of 78 and 60 studies (Berghaus 2011 & Berghaus 1995, respectively)(22, 23)
   b. Many medium-to-high quality findings from placebo-controlled experimental studies (Ramaekers 2009, Ramaekers & Kauert 2006, Ramaekers & Moeller 2006, Kelly 1993, Hunault 2009, Curran 2002, Ronen 2008, Lenne 2010)(9, 19, 24, 27-31)
   c. Few findings of no impairment (Hart 2001, Schwope 2012, Ronen 2010).(8, 17, 32) These studies used lower doses, chronic users, and/or relatively insensitive performance measures.

2. Evidence details

   a. Berghaus et al (2011) in a meta-analysis of 78 studies (all published after 1993) found that > 50% of performance test results were impaired at all three smoked dose categories of 1 to < 9 mg, 9 to < 18 mg, and 18 to 52 mg.(22) The authors attributed the lack of a dose-response effect to the variable smoking topography and self-titration of dose. In contrast, a dose-response effect was shown for oral THC at the same dose categories in the same meta-analysis. There was a dose-response effect for impairment vs. THC blood levels after smoking marijuana in this meta-analysis.
   b. Berghaus et al (1995) in a meta-analysis of 60 studies found that 69-80% of performance test results were

impaired 1 hr after smoking a median THC dose of 10.7 mg.(23)

c. Some studies show dose-related performance decrements compared to placebo starting at doses as low as 3-7 mg smoked THC, but many studies show significant decrements at > 13-14 mg.(9, 19, 24, 27-31, 33)

d. The relatively few experimental studies that have not shown significant impairment after smoking marijuana have tended to use lower doses (<14 mg), subjects who are chronic users, and/or performance measures that are relatively insensitive to the effects of marijuana.(8, 17, 21, 32)

b. By oral ingestion:

i. **EVIDENCE STATEMENT 4: We found moderate evidence that ingesting more than about 15 mg THC <u>is capable of</u> yielding a whole blood THC concentration > 5 ng/mL.**

1. Evidence summary

a. Difficult to rate evidence due to high inter-individual variability in GI absorption and first-pass metabolism and different substrates used in studies.

b. A limited review of pharmacokinetic literature was done.

c. 2 high quality findings (Menetrey 2005, Lile 2013)(10, 34)

d. 1 supporting finding (Huestis 2007 review)(2)

e. 3 opposing findings [Bosker 2012 (high quality) Curran 2002 (high quality), Huestis 2007 review](2, 29, 35)

2. Evidence details

a. Systemic doses are highly variable due to inter-individual differences in GI absorption and first-pass metabolism.(2, 14)

b. Menetrey et al found mean peak whole blood THC concentrations of 2.8 ng/mL (range non-detectable to 5.6) after dronabinol 20 mg, 3.8 ng/mL (range 1.5-8.3) after milk decoction containing 16.5 mg THC, and 8.4 ng/mL (range 3.9-13.1) after milk decoction containing 45.7 mg THC.(10) See **Figures 2** and **4** in the Appendix.

c. Lile et al showed that mean peak whole blood THC levels exceeded 5 ng/mL only at oral doses $\geq$ 45 mg. However, there was large inter-individual variability, and some subjects yielded levels > 5 ng/mL at doses of 15 mg and 30 mg.(34) See **Figures 5** and **6** in the Appendix.

d. Bosker et al found that peak whole blood THC levels did not reach 5 ng/mL in occasional users after 10 mg or 20 mg of dronabinol.(35) However, the blood sampling may have missed the time of peak concentration because it was done at 1.5 hrs and then not again until 4.25 hrs post-dosing. The highest mean levels were 3.1 ng/mL in the 20 mg group and 1.6 ng/mL in the 10 mg group, both at 1.5 hrs.

e. One study demonstrated peak whole blood THC concentrations of 2.2-5.5 ng/mL at 1-5 hrs after ingesting a chocolate cookie containing 20 mg THC. (2)

f. Another study found peak whole blood THC concentrations < 3.3 ng/mL after 7.5 mg or 14.8 mg THC in hemp oil in three divided doses with meals over a day.(2)

ii. **EVIDENCE STATEMENT 5: We found substantial evidence that, for occasional users, ingesting 10 mg or more of THC is likely to meaningfully impair driving ability.**

1. Evidence summary

   a. 1 high quality finding from a meta-analysis of 21 experimental studies (Berghaus 2011)(22)

   b. 1 high quality finding from an experimental study (Bosker 2012)(35)

   c. 2 medium quality findings from experimental studies (Menetrey 2005, Curran 2002)(10, 29)

   d. No opposing findings in occasional users

2. Evidence details

   a. Berghaus et al in their meta-analysis (2011) of 21 studies of oral marijuana and driving impairment demonstrated a dose-response effect on impairment.(22) Only 10% of performance test results were impaired at THC doses of 7.5 to < 9 mg. Forty-one percent of test results were impaired at doses of ≥ 9 to < 18, and 55% were impaired at doses of ≥ 18 to 39.

   b. Bosker et al tested on-road driving in occasional users 2-4 hrs after dronabinol 10 mg, dronabinol 20 mg or placebo.(35) The 10 mg and 20 mg groups showed impairment equivalent to 0.05% BAC and 0.08% BAC, respectively.

   c. Menetrey et al tested performance on psychomotor tasks and simulated driving in occasional users after dronabinol 20 mg, milk decoction containing 16.5 mg THC, or milk decoction containing 45.7 mg THC.(10)

Impairment was statistically significant for all 3 dose groups compared to placebo and was greatest at 1-5.5 hrs post-ingestion.

    d. Curran et al tested performance on cognitive tests relevant to driving in infrequent users after dronabinol 7.5 mg or 15 mg or placebo.(29) Impairment was greatest at 1-2 hrs post-dosing (corresponding to peak THC levels) and greater in the high-dose than the low-dose group.

c. By vaporization:

    i. **EVIDENCE STATEMENT 6: We found moderate evidence that inhaling vaporized marijuana yields blood THC levels that are similar to those produced by smoking the same dose.**

        1. Evidence summary

            a. 1 high quality finding (Abrams 2007)(12)

            b. No opposing findings

        2. Evidence details

            a. Abrams et al. found similar plasma concentrations of THC by vaporization and smoking through 360 minutes post-dosing, except for higher concentrations by vaporization at 30 and 60 minutes.(12) Peak plasma concentrations (at 2 minutes) and systemic doses (area under the concentration–time curves) were not significantly different. See **Figure 7** in the Appendix. Subjective effects were similar between the vaporizing subjects and the smoking subjects. Performance effects were not examined.

            b. Plasma concentrations of THC are similar to those obtained by smoking, but bioequivalence has not been fully established.(5, 12)

3. *Are blood THC levels in marijuana-impaired drivers higher now than in the past? (1 evidence statement)*

    a. **EVIDENCE STATEMENT 7: We found moderate evidence that blood THC levels of marijuana-impaired drivers are higher now than in the past.**

        i. Evidence summary

            1. 1 high quality finding (Vindenes 2013)(36)

        ii. Evidence details

            1. Vindenes et al found a 58% increase in the mean whole blood THC concentrations of Norwegian drivers suspected of drugged driving who tested negative for alcohol and other drugs during the period from 2000 to 2010.(36) Mean levels

increased from 4.0 (± 0.3) ng/mL in 2000 to 6.6 (± 0.4) ng/mL in 2010.

4. *How long do you need to wait to drive unimpaired after becoming high from marijuana? (6 evidence statements)*
   a. After smoking:
      i. **EVIDENCE STATEMENT 8: We found substantial evidence that delaying driving at least 6 hours after smoking less than 18 mg THC allows THC-induced impairment to resolve or nearly resolve for occasional users.**
         1. Evidence summary
            a. 2 high quality findings from 2 meta-analyses of 78 and 60 experimental studies (Berghaus 2011 and 1995, respectively)(22, 23)
         2. Evidence details
            a. Berghaus et al (2011) in a meta-analysis of 78 studies (published after 1993) found that the percentage of impaired performance test results was greatest in the first hour after smoking and decreased to < 15% (the cutoff for impairment) at a mean 2.5 hrs (range 2.5-4.0) and 4.75 hrs (range 3.75-5.75) for doses of 1 to < 9 mg and > 9 to < 18 mg THC, respectively.(22) See **Figure 8** in Appendix.
            b. Berghaus et al (1995) in a meta-analysis of 60 studies found that the percentage of impaired performance test results was greatest in the first 2 hours after smoking but resolved or nearly resolved by 5 hrs post-smoking after a median dose of 10.7 mg THC.(23)
            c. Most experimental studies have shown the greatest performance deficits within the first 1-2 hours after smoking THC and lasting for 3-6 hours.(9, 21, 24, 38)

      ii. **EVIDENCE STATEMENT 9: We found moderate evidence that delaying driving at least 6 hours after smoking about 35 mg THC allows THC-induced impairment to resolve or nearly resolve for occasional users.**
         1. Evidence summary
            a. 3 medium quality findings from 3 experimental studies (Ramaekers 2009; Ramaekers, Kauert et al 2006, Hunault 2009)(9, 19, 28)
         2. Evidence details
            a. Both Ramaekers studies used 500 mcg/kg (35 mg/70 kg) doses and found statistically significant

performance impairment on some psychomotor tests repeated over 6-8 hrs post-smoking. Impairment appeared to resolve or nearly resolve by 6 hrs post-smoking (See **Figure 9** in Appendix), but significance testing was not done separately at each time point to allow determination of when differences become non-significant. Effect sizes were small to moderate in Ramaekers, Kauert et al 2006 and were not reported in Ramaekers 2009.

b. Hunault et al (2009) reported dose-related slowed reaction time in 24 occasional and moderate (2-9 joints per month) users at 29.3, 49.1 and 69.4 mg THC compared to placebo.(28) Mean reaction time on serial testing approached placebo-level but was still 10-13% slower than placebo (a statistically significant difference) at 5 hrs post-smoking for all 3 dose groups. The investigators did not repeat testing after 5 hrs to determine the time when impairment of reaction time resolved. Large inter-individual variability in motor impairment at the same doses was observed. No other psychomotor tests were performed serially to assess duration of impairment.

iii. **EVIDENCE STATEMENT 10: We found insufficient evidence to determine the amount of time necessary to wait after smoking more than 35 mg THC to allow THC-induced impairment to resolve for occasional users.**

1. Evidence summary

a. We found no studies that examine duration of driving impairment (through the point of resolution of impairment) after smoking > 35 mg THC.

b. Very few studies have used high smoked doses and done serial performance testing over enough time to identify the earliest time point at which performance reaches baseline or becomes no different from placebo. Hunault et al tested psychomotor performance in occasional and moderate users (2-9 joints per month) after smoking up to 69 mg THC, but the investigators did not repeat testing long enough to determine the time when impairment resolved.(28) Impairment of reaction time was still statistically significant compared to placebo at 5 hrs post-smoking.

c. Those studies that have used higher doses and serial performance testing have not reported significance testing at time points where performance appears to approach baseline/placebo level. Berghaus et al in their 2011 meta-analysis were unable to determine a duration of impairment at doses > 18 mg because of too few data.(22)

b. After oral ingestion:
   i. **EVIDENCE STATEMENT 11: We found substantial evidence that delaying driving at least 8 hrs after oral ingestion of < 18 mg THC allows THC-induced impairment to resolve or nearly resolve for occasional users.**
      1. Evidence summary
         a. 1 high quality finding from a meta-analysis of 21 experimental studies (Berghaus 2011)(22)
         b. 1 medium quality finding (Menetrey 2005)(10)
         c. 1 low quality finding (Curran 2002)(29)
         d. Other supporting evidence for waiting 8 hrs (instead of 5 or 6)
            i. GI absorption is variable, peak of effects is delayed and duration of effects is longer with ingestion than with smoking.(Huestis 2007 review)(2)
      2. Evidence details
         a. Berghaus et al in a meta-analysis of 21 studies found that the percentage of impaired performance test results was greatest in the first 1-2 hrs and decreased to < 15% (the cutoff for impairment) at a mean 5.0 hours (range 4.25-5.75) for oral doses of > 9 to < 18 mg.(22) (See **Figure 10** in Appendix.)
         b. Menetrey et al found tested psychomotor performance in occasional users after 20 mg dronabinol, 16.5 mg THC milk decoction, and 45.7 mg THC milk decoction.(10) Impairment for all three dose groups on a tracking test was greatest through 5 hrs post-ingestion, with the two lower dose groups' performance approaching the placebo group's performance by 7.5 hrs. The 47.5 mg group's performance impairment appeared to persist longer. (See **Figure 11** in

Appendix.) The authors did not report at what time point the differences between each treatment group and placebo became statistically non-significant.

c. Curran et al found cognitive performance in subjects who received 7.5 mg and 15 mg dronabinol, respectively.(29) Performance on a variety of cognitive and psychomotor tasks was tested serially over 8 hrs and then again at 24 and 48 hrs post-dosing. Impairment was evident on some tasks and was greatest at 2 hrs. The presentation of the results does not make it clear when impairment resolved on the various tasks, but the authors report that "no significant effects of THC on any measure were evident 24 or 48 h" post-dosing. Many of the tasks used in this study are not relevant to driving.

c. EVIDENCE STATEMENT 12: **We found insufficient evidence to determine the amount of time necessary to delay driving to allow THC-induced impairment to resolve or nearly resolve <u>for regular or heavy users</u> after smoking, vaporizing, or oral ingestion of marijuana.**

  i. Tolerance to acute effects in heavy users has been clearly demonstrated, but uncertainty exists regarding the extent to which tolerance mitigates impairment or duration of impairment in highly complex tasks or safety sensitive tasks such as driving.(8, 17-21)

d. After other methods of marijuana use:

  i. **EVIDENCE STATEMENT 13: We found insufficient evidence to determine the amount of time to delay driving after other methods of marijuana use (vaporizing and application of dermal and mucosal preparations) for occasional, regular, or heavy users.**

    1. Evidence summary

      a. We found no studies on vaporized marijuana or dermal or mucosal marijuana preparations and effects on driving or psychomotor skills.

5. *Can one screen positive for marijuana from passive exposure to marijuana smoke? (2 evidence statements)*

  a. **EVIDENCE STATEMENT 14: We found substantial evidence that an individual passively exposed to marijuana smoke (up to approximately 10% THC) under <u>usual</u> passive exposure conditions would NOT test**

positive for marijuana on a urine screening test or a blood test, given the current federal screening cutoff (50 ng/mL for urine cannabinoid metabolites) and the current Colorado limit for driving (5 ng/mL whole blood THC).

    i. Evidence summary

        1. 5 high quality findings [Cone 2014, Niedbala 2004, Niedbala 2005 (2 findings published in the same paper), Rohrich 2010]

        2. While THC and cannabinoid metabolites are detectable in blood and urine, respectively, they do not reach current screening cutoffs under usual exposure conditions and rarely under extreme exposure conditions.

        3. Several opposing findings from 1980s using extreme exposure conditions

    ii. Evidence details

        1. Some early experimental studies of THC and cannabinoid metabolite levels in blood and urine after passive exposure demonstrated significant levels, often above commonly used screening cutoffs.(37-39) These studies used extreme conditions of very high exposure in small unventilated spaces and, in some cases, repetitive exposure. Morland et al commented that all of their participants, active and passive, reported discomfort from the thick marijuana smoke, suggesting that individuals would be unlikely to willingly subject themselves to such conditions in the real world.(39) Other early studies that used more realistic exposure conditions found low to undetectable levels which were below screening cutoffs.(40-43) Besides differences in experimental conditions, comparison of results of early studies is complicated by variability in performance characteristics among different urine tests used.(41)

        2. More recent studies have found detectable but low levels of THC and cannabinoid metabolites in serum and urine after realistic to extreme passive exposure.(44-47) Rohrich et al found a mean peak whole blood THC concentration of 0.25 ng/mL (range 0-0.35 ng/mL) after 3 hrs of passive exposure in a well-attended Dutch coffee shop.(44) The mean peak urine "cannabinoid equivalent" concentration by immunoassay was 16 ng/mL (range 13-20 ng/mL), and the mean peak urine THC-COOH concentration by GC-MS was 2.3 ng/mL before hydrolysis (range < LOQ to 4.8 ng/mL) and 3.8 ng/mL after hydrolysis (range 1.3-4.8 ng/mL). All of the urine values were well below both the screening cutoff in the U.S. of 50 ng/mL

(all cannabinoid metabolites) and the confirmation cutoff of 15 ng/mL (THC-COOH only).(48) The whole blood THC values were all well below 5 ng/mL, Colorado's legal limit for driving. Niedbala et al in 3 studies of extreme passive exposure reported all screening and confirmation urine tests through 4 to 72 hours to be negative at the above cutoff levels.(45, 46) The single highest THC-COOH confirmation test level was 14.7 ng/mL, but the corresponding screening urine test was negative.(46) Therefore, in practice the confirmation test would not have been done. A very recent study by Cone et al examined urine cannabinoids by immunoassay and urine THC-COOH by GC-MS after passive exposure to smoke from 5.3% THC joints in an unventilated smoking chamber (10 x 13 x 7 feet) and also to smoke from 11.3% THC joints under unventilated and unventilated conditions in the same chamber.(47) No urine specimen exceeded the 50 ng/mL screening cutoff in the 5.3% THC unventilated group or the 11.3% ventilated group. A single specimen collected at 4 hrs post-exposure screened positive at the 50 ng/mL cutoff in the 11.3% THC unventilated group. The overall positivity rate at the 50 ng/mL cutoff was 0.4%. Of note, after the first session of this study using the 5.3% THC joints in the unventilated chamber, study participants (both smokers and non-smokers) had to be supplied with goggles due to complaints of eye irritation. This again suggests that individuals would not willingly tolerate such conditions in the real world.

b. **EVIDENCE STATEMENT 15: We found insufficient evidence to determine whether individuals passively exposed to marijuana smoke would screen positive by oral fluid testing because it has not yet been established which analyte or analytes to measure and which cutoff(s) to use.**

   i. Evidence details: Oral fluid testing is being considered as a potential marijuana use screening test in the workplace or by law enforcement.(49-51) Both THC and THC-COOH can be measured in oral fluid, and it has been proposed that THC-COOH should be measured in conjunction with THC to avoid false positives from passive exposure.(49, 51) However, THC is the usual target analyte in oral fluid. Some relatively recent studies have measured oral fluid THC and cannabinoid concentrations in passively exposed subjects.(45, 46, 49) Niedbala et al in an initial study found that oral fluid THC tests may be transiently positive on both screening and confirmation for up to about 30 minutes after fairly high passive exposure.(45) A follow-up study by the same group using more extreme exposure conditions revealed that oral fluid collection

devices became contaminated if used in the presence of ambient marijuana smoke, leading to false positive tests.(46) When oral fluid specimens were collected outside of the smoky area, passively exposed subjects' oral fluid specimens were negative for THC on both oral fluid screening and confirmation tests. By contrast, Moore et al found that all subjects passively exposed in 2 Dutch coffee shops had detectable THC in the oral fluid 3 hrs after exposure, with half having levels > 4 ng/mL, a proposed cutoff level. However, THC-COOH was not detected in any of the specimens. The authors concluded that THC-COOH should be tested in conjunction with THC in oral fluid to avoid false positives. Unlike the studies by Niedbala et al, this study did not include an actively exposed control group.(49) Different oral fluid THC cutoff levels were used by Niedbala et al (3 ng/mL) and Moore et al (4 ng/mL).

6. *How long does it take to feel the full effects of an ingested marijuana product ?*

   a. **EVIDENCE STATEMENT 16: We found <u>substantial</u> evidence that it takes up to 4 hours after ingesting marijuana to achieve peak blood or plasma concentrations.**

      i. Evidence summary

         1. 4 medium quality findings [Menetrey 2005, Curran 2002 , Bosker 2012, Lile 2013]

         2. THC levels and impairment are not synonymous, peak THC levels precede functional impairment.

         3. Higher doses are difficult to study due to adverse side effects (nausea and vomiting).

      ii. Evidence details

         1. Menetrey 2005: Double-blind crossover study, 8 males (22-30 years) all occasional cannabis users. No other drug use. All were required to abstain from drug and alcohol use one week prior to study. Two week washout between study periods. Highest mean concentration of THC was achieved 1 hour after ingestion of highest dose decoction. Small sample size (8 subjects, crossover design).(10) See **Figures 2 and 4** in the Appendix.

         2. Curran 2002: Cross-over design with placebo, 7.5 mg and 15 mg capsules of THC.   Fifteen healthy male volunteers 18-30 years old (mean 24.2). Occasional users with no other drug use were selected. Volunteers abstained for three weeks prior to testing. Measured THC levels at 1, 2, 4, 6 ,8, 24, and 48 hours. Reported peak plasma concentrations at two hours post

ingestion, with a mean peak for 15 mg dose of approximately 4.75 ng/mL and a mean peak for 7.5 mg dose of approximately 1.25 ng/mL. (29)

3. Bosker 2012: Double-blind, placebo-controlled, three-way crossover.   Twelve occasional and twelve heavy users(14 males, 10 females). Administered placebo, 10 mg, and 20 mg dronabinol.   Peak concentration is achieved within 2-4 hours after oral administration. Concentrations may remain on plateau for up to 6 hours post ingestion.   Findings: Peak THC concentrations at 1.5 hours (tested 1.5, 4.25, 6 hours post ingestion). (35)

4. Lile 2013:Blinded, placebo-controlled, dose run-up crossover design. Seven subjects who were regular cannabis users. Doses: placebo, 15, 30, 45, 60, 75, and 90 mg oral THC, adminstered in 15 mg increments in escalating fashion. Each dose was treated as a single separate experimental observation performed in a single 24 hour visit. Time between sessions was at least 48 hours, median 7 days. Two subjects dropped out at higher concentrations due to nausea and vomiting. No other adverse reactions were noted.   Doses produced physiologic (elevated heart rate) and behavioral effects reported previously. Peak plasma THC concentrations occurred between 2 and 4 hours post-ingestion. (34) See **Figure 12** in the Appendix.

7. *What drugs are likely to have significant adverse interactions if used concomitantly with marijuana? (2 evidence statements)*

   a. **EVIDENCE STATEMENT 17: Biological evidence shows the combination of marijuana and alcohol or another sedating drug will cause greater impairment than that caused by marijuana, alcohol or the other drug used separately.**

   b. **EVIDENCE STATEMENT 18: Clinical and pharmacokinetic data about marijuana's interactions with other drugs are limited at this time and are likely to evolve substantially over coming years. There is credible evidence of clinically important drug-drug interactions with marijuana, including the following: chlorpromazine, clozapine, CNS depressants, disulfiram, hexobarbital, hydrocortisone, indinavir, ketoconazole, MAO inhibitors, phenytoin, theophylline, and warfarin. The lack of a cited interaction does not preclude the possibility that drug interactions exist; it simply means that no studies have yet reported an interaction with that particular drug.**

i. It is reasonable to assume that any drug with CNS depressant effects taken concomitantly with marijuana is likley to enhance the CNS depressant effects of marijuana.(52)

ii. No clinically significant drug-drug interactions were found in the clinical trials of Marinol.(52) Concomitant drugs included cytotoxic agents, anti-infective agents, sedatives, and opioid analgesics.

iii. From a public health perspective, the most common and significant adverse drug interaction of marijuana is with alcohol due to enhanced CNS depressant effect, additive driving impairment and markedly increased crash risk.(20, 21, 53-56)

iv. Specific concomitant drugs/drug classes with clinical evidence for potential interactions are shown in **Table 3** in the Appendix. **Table 3** also includes three drugs (fluoxetine, nelfinavir, and omeprazole) for which there is published clinical evidence of an <u>absence</u> of interaction with marijuana. **(5,52,55,58-70)**

REFERENCES

1.   Morris M. Data on typical THC content of retail marijuana from a CDPHE informal telephone survey of Denver marijuana dispensaries. 2014.

2.   Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers. 2007;4(8):1770-804.

3.   Grotenhermen F, Leson G, Berghaus G, Drummer OH, Kruger HP, Longo M, et al. Developing limits for driving under cannabis. Addiction. 2007;102(12):1910-7.

4.   Light MK, Orens A, Lewandowski B, Pickton T. Market size and demand for marijuana in Colorado. Colorado Department of Revenue; 2014.

5.   Abramovici H. Information for Health Care Professionals. In: Canada H, editor. 2013.

6.   Ramesh D, Haney M, Cooper ZD. Marijuana's dose-dependent effects in daily marijuana smokers. Exp Clin Psychopharmacol. 2013;21(4):287-93.

7.   Pleuvry BJ. Hysteresis in drug response. *Anaesthesia & Intensive Care Medic*ine 2005;6(8):286-7.

8.   Schwope DM, Bosker WM, Ramaekers JG, Gorelick DA, Huestis MA. Psychomotor performance, subjective and physiological effects and whole blood Delta(9)-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. J Anal Toxicol. 2012;36(6):405-12.

9.   Ramaekers JG, Kauert G, van Ruitenbeek P, Theunissen EL, Schneider E, Moeller MR. High-potency marijuana impairs executive function and inhibitory motor control. Neuropsychopharmacology. 2006;31(10):2296-303.

10.   Menetrey A, Augsburger M, Favrat B, Pin MA, Rothuizen LE, Appenzeller M, et al. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg dronabinol or of a cannabis decoction made with 20 or 60 mg Delta9-THC. J Anal Toxicol. 2005;29(5):327-38.

11.   Heishman SJ, Stitzer ML, Yingling JE. Effects of tetrahydrocannabinol content on marijuana smoking behavior, subjective reports, and performance. Pharmacol Biochem Behav. 1989;34(1):173-9.

12.   Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther. 2007;82(5):572-8.

13.   Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther. 1992;52(1):31-41.

14.   Perez-Reyes M, Lipton MA, Timmons MC, Wall ME, Brine DR, Davis KH. Pharmacology of orally administered 9 -tetrahydrocannabinol. Clin Pharmacol Ther. 1973;14(1):48-55.

15.   Micromedix 2.0: Dronabinol.

16.   ICI Americas Inc. The HLB system: a time-saving guide to emulsifier selection. Wilmington, Delaware1976.

17.   Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. Neuropsychopharmacology. 2001;25(5):757-65.

18.   Bosker WM, Karschner EL, Lee D, Goodwin RS, Hirvonen J, Innis RB, et al. Psychomotor function in chronic daily Cannabis smokers during sustained abstinence. PLoS One. 2013;8(1):e53127.

19.   Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. J Psychopharmacol. 2009;23(3):266-77.

20.   Wolff K, Johnston A. Cannabis use: a perspective in relation to the proposed UK drug-driving legislation. Drug Test Anal. 2014;6(1-2):143-54.

21.   Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem. 2013;59(3):478-92.

22.   Berghaus G, Sticht G, Grellner W. Meta-analysis of empirical studies concerning the effects of medicines and illegal drugs including pharmacokinetics on safe driving. Center for Traffic Sciences at the University of Wurzburg, 2011.

23.   Berghaus G, Scheer N, Schmidt P. Effects of cannabis on psychomotor skills and driving performance - a metaanalysis of experimental studies 1995 [cited 2014 8/31/2014]. Available from: http://casr.adelaide.edu.au/T95/paper/s16p2.html.

24.   Ramaekers JG, Moeller MR, van Ruitenbeek P, Theunissen EL, Schneider E, Kauert G. Cognition and motor control as a function of Delta9-THC concentration in serum and oral fluid: limits of impairment. Drug Alcohol Depend. 2006;85(2):114-22.

25.   Reeve VC, Grant JD, Robertson W, Gillespie HK, Hollister LE. Plasma concentrations of delta-9-tetrahydrocannabinol and impaired motor function. Drug Alcohol Depend. 1983;11(2):167-75.

27.   Kelly TH, Foltin RW, Emurian CS, Fischman MW. Performance-based testing for drugs of abuse: dose and time profiles of marijuana, amphetamine, alcohol, and diazepam. J Anal Toxicol. 1993;17(5):264-72.

28.   Hunault CC, Mensinga TT, Bocker KB, Schipper CM, Kruidenier M, Leenders ME, et al. Cognitive and psychomotor effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg delta-9-tetrahydrocannabinol (THC). Psychopharmacology (Berl). 2009;204(1):85-94.

29.   Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology (Berl). 2002;164(1):61-70.

30.   Ronen A, Gershon P, Drobiner H, Rabinovich A, Bar-Hamburger R, Mechoulam R, et al. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. Accid Anal Prev. 2008;40(3):926-34.

31.   Lenne MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. Accid Anal Prev. 2010;42(3):859-66.

32.   Ronen A, Chassidim HS, Gershon P, Parmet Y, Rabinovich A, Bar-Hamburger R, et al. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accid Anal Prev. 2010;42(6):1855-65.

33.   Weinstein A, Brickner O, Lerman H, Greemland M, Bloch M, Lester H, et al. A study investigating the acute dose-response effects of 13 mg and 17 mg Delta 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. J Psychopharmacol. 2008;22(4):441-51.

34.   Lile JA, Kelly TH, Charnigo RJ, Stinchcomb AL, Hays LR. Pharmacokinetic and pharmacodynamic profile of supratherapeutic oral doses of Delta(9) -THC in cannabis users. J Clin Pharmacol. 2013;53(7):680-90.

35.   Bosker WM, Kuypers KP, Theunissen EL, Surinx A, Blankespoor RJ, Skopp G, et al. Medicinal Delta(9) -tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in Standard Field Sobriety Tests. Addiction. 2012;107(10):1837-44.

36.   Vindenes V, Strand DH, Kristoffersen L, Boix F, Morland J. Has the intake of THC by cannabis users changed over the last decade? Evidence of increased exposure by analysis of blood THC concentrations in impaired drivers. Forensic Sci Int. 2013;226(1-3):197-201.

37.   Cone EJ, Johnson RE, Darwin WD, Yousefnejad D, Mell LD, Paul BD, et al. Passive inhalation of marijuana smoke: urinalysis and room air levels of delta-9-tetrahydrocannabinol. J Anal Toxicol. 1987;11(3):89-96.

38.   Cone EJ, Johnson RE. Contact highs and urinary cannabinoid excretion after passive exposure to marijuana smoke. Clin Pharmacol Ther. 1986;40(3):247-56.

39.   Morland J, Bugge A, Skuterud B, Steen A, Wethe GH, Kjeldsen T. Cannabinoids in blood and urine after passive inhalation of Cannabis smoke. J Forensic Sci. 1985;30(4):997-1002.

40.   Law B, Mason PA, Moffat AC, King LJ, Marks V. Passive inhalation of cannabis smoke. J Pharm Pharmacol. 1984;36(9):578-81.
41.   Mule SJ, Lomax P, Gross SJ. Active and realistic passive marijuana exposure tested by three immunoassays and GC/MS in urine. J Anal Toxicol. 1988;12(3):113-6.
42.   Perez-Reyes M, di Guiseppi S, Davis KH. Passive inhalation of marijuana smoke and urinary excretion cannabinoids. Jama. 1983;249(4):475.
43.   Mason AP, Perez-Reyes M, McBay AJ, Foltz RL. Cannabinoids in plasma after passive inhalation of marijuana smoke. Jama. 1983;249(4):475-6.
44.   Rohrich J, Schimmel I, Zorntlein S, Becker J, Drobnik S, Kaufmann T, et al. Concentrations of delta9-tetrahydrocannabinol and 11-nor-9-carboxytetrahydrocannabinol in blood and urine after passive exposure to Cannabis smoke in a coffee shop. J Anal Toxicol. 2010;34(4):196-203.
45.   Niedbala S, Kardos K, Salamone S, Fritch D, Bronsgeest M, Cone EJ. Passive cannabis smoke exposure and oral fluid testing. J Anal Toxicol. 2004;28(7):546-52.
46.   Niedbala RS, Kardos KW, Fritch DF, Kunsman KP, Blum KA, Newland GA, et al. Passive cannabis smoke exposure and oral fluid testing. II. Two studies of extreme cannabis smoke exposure in a motor vehicle. J Anal Toxicol. 2005;29(7):607-15.
47.   Cone EJ, Bigelow GE, Herrmann ES, Mitchell JM, LoDico C, Flegel R, et al. Non-Smoker Exposure to Secondhand Cannabis Smoke. I. Urine Screening and Confirmation Results. J Anal Toxicol. 2014.
48.   Norchem Lab. Urine Drug Test Information Sheet: Marijuana [8/8/2014]. Available from: http://www.norchemlab.com/wp-content/uploads/2011/10/marijuana.pdf.
49.   Moore C, Coulter C, Uges D, Tuyay J, van der Linde S, van Leeuwen A, et al. Cannabinoids in oral fluid following passive exposure to marijuana smoke. Forensic Sci Int. 2011;212(1-3):227-30.
50.   Walsh JM, Cone EJ, Crouch DJ, Caplan YH. Is THC-COOH a useful determinant for passive inhalation in oral fluid THC testing? J Anal Toxicol. 36. United States2012. p. 291.
51.   Moore C. Response to "Is THCCOOH a useful determinant for passive inhalation in oral fluid THC testing?". J Anal Toxicol. 36. United States2012. p. 358.
52.   Unimed Pharmaceuticals. Marinol (Dronabinol) package insert. 2004.
53.   Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. Bmj. 2012;344:e536.
54.   Ramaekers JG, Berghaus G, van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend. 2004;73(2):109-19.
55.   Lexi-Comp Online. Interaction Lookup.
56.   Reisfield GM. Medical cannabis and chronic opioid therapy. J Pain Palliat Care Pharmacother. 2010;24(4):356-61.
57.   Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol. 1992;16(5):276-82.
58.   Chetty M, Miller R, Moodley SV. Smoking and body weight influence the clearance of chlorpromazine. Eur J Clin Pharmacol. 1994;46(6):523-6.
59.   Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. Int Clin Psychopharmacol. 2002;17(3):141-3.
60.   Cornelius JR, Bukstein OG, Douaihy AB, Clark DB, Chung TA, Daley DC, et al. Double-blind fluoxetine trial in comorbid MDD-CUD youth and young adults. Drug Alcohol Depend. 2010;112(1-2):39-45.
61.   Benowitz NL, Nguyen TL, Jones RT, Herning RI, Bachman J. Metabolic and psychophysiologic studies of cannabidiol-hexobarbital interaction. Clin Pharmacol Ther. 1980;28(1):115-20.
62.   D'Souza DC, Ranganathan M, Braley G, Gueorguieva R, Zimolo Z, Cooper T, et al. Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis. Neuropsychopharmacology. 2008;33(10):2505-16.

63.   Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. Aids. 2002;16(4):543-50.

64.   Stott C, White L, Wright S, Wilbraham D, Guy G. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. Springerplus. 2013;2(1):236.

65.   Jessen K. Recreational use of phenytoin, marijuana, and alcohol: a case report. Neurology. 2004;62(12):2330.

66.   Bland TM, Haining RL, Tracy TS, Callery PS. CYP2C-catalyzed delta9-tetrahydrocannabinol metabolism: kinetics, pharmacogenetics and interaction with phenytoin. Biochem Pharmacol. 2005;70(7):1096-103.

67.   Gardner MJ, Tornatore KM, Jusko WJ, Kanarkowski R. Effects of tobacco smoking and oral contraceptive use on theophylline disposition. Br J Clin Pharmacol. 1983;16(3):271-80.

68.   Jusko WJ, Gardner MJ, Mangione A, Schentag JJ, Koup JR, Vance JW. Factors affecting theophylline clearances: age, tobacco, marijuana, cirrhosis, congestive heart failure, obesity, oral contraceptives, benzodiazepines, barbiturates, and ethanol. J Pharm Sci. 1979;68(11):1358-66.

69.   Yamreudeewong W, Wong HK, Brausch LM, Pulley KR. Probable interaction between warfarin and marijuana smoking. Ann Pharmacother. 2009;43(7):1347-53.

70.   Ge B, Zhang Z, Zuo Z. Updates on the clinical evidenced herb-warfarin interactions. Evid Based Complement Alternat Med. 2014;2014:957362.

APPENDIX

Figure 1. Plasma THC vs. time in 6 subjects during and after smoking a single marijuana cigarette of 3.55% THC using a paced smoking protocol. From Huestis et al 1992 (57)
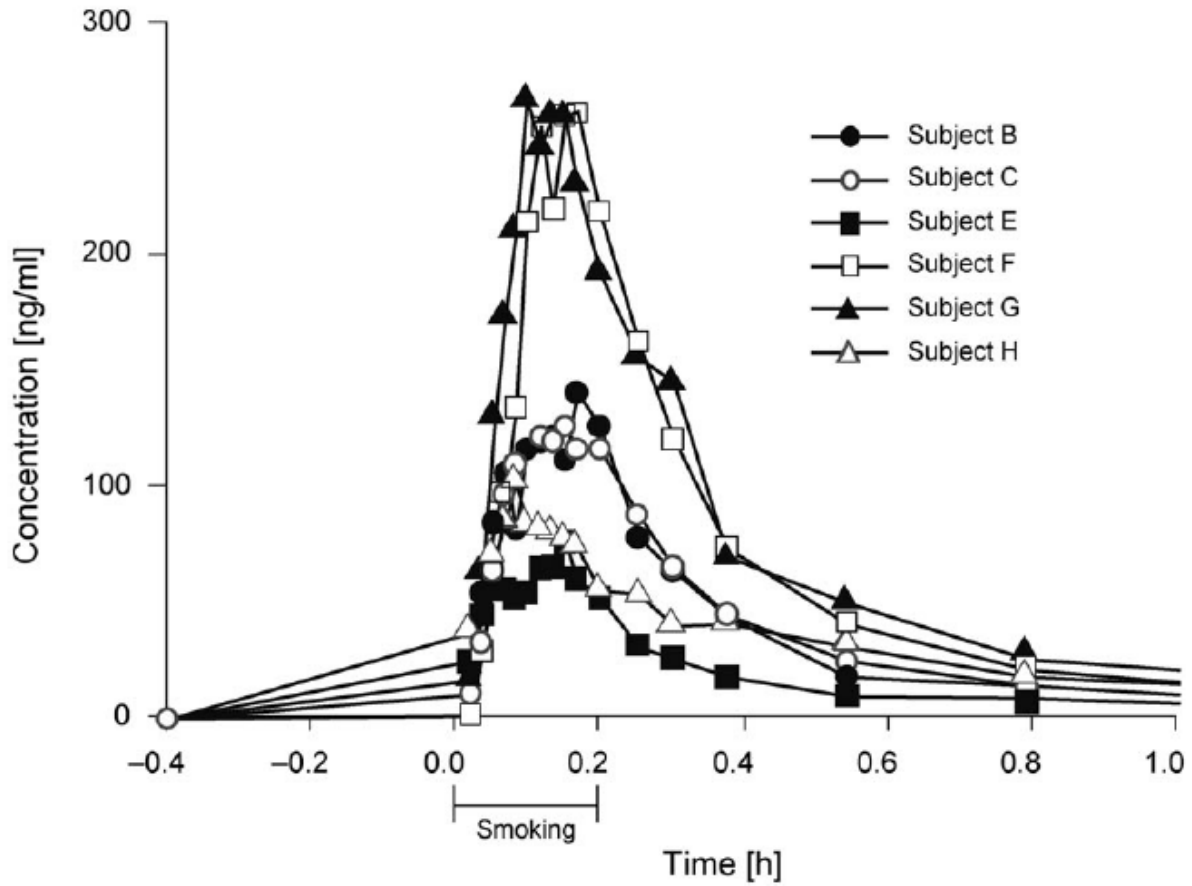
Figure 2. Whole blood THC vs. time in 8 subjects after ingesting 45.7 mg THC in a milk decoction. From Menetrey 2005. (10)
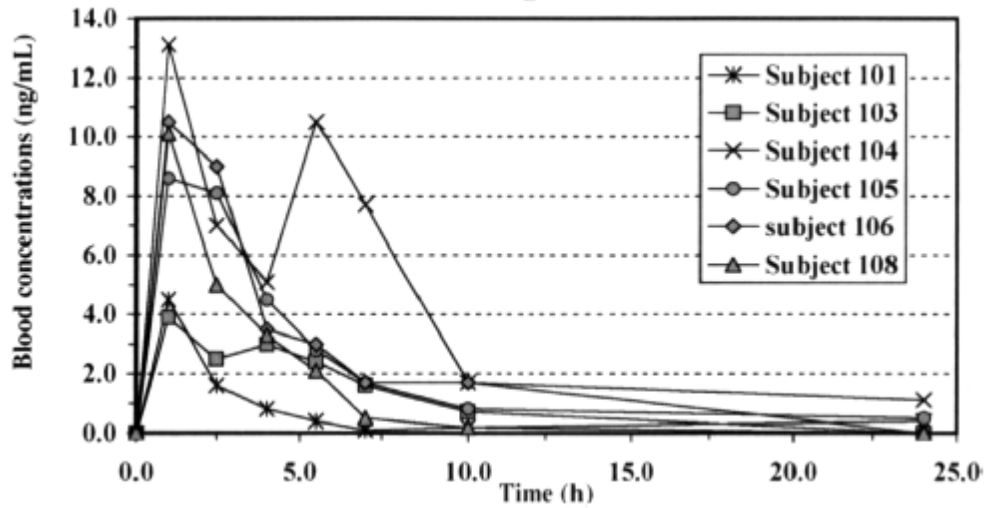
Figure 3. Mean plasma THC concentrations (ng/mL) vs. time (hrs) during and after smoking a single THC (1.75% or 3.55%) cigarette. From Huestis et al (1992).(57)
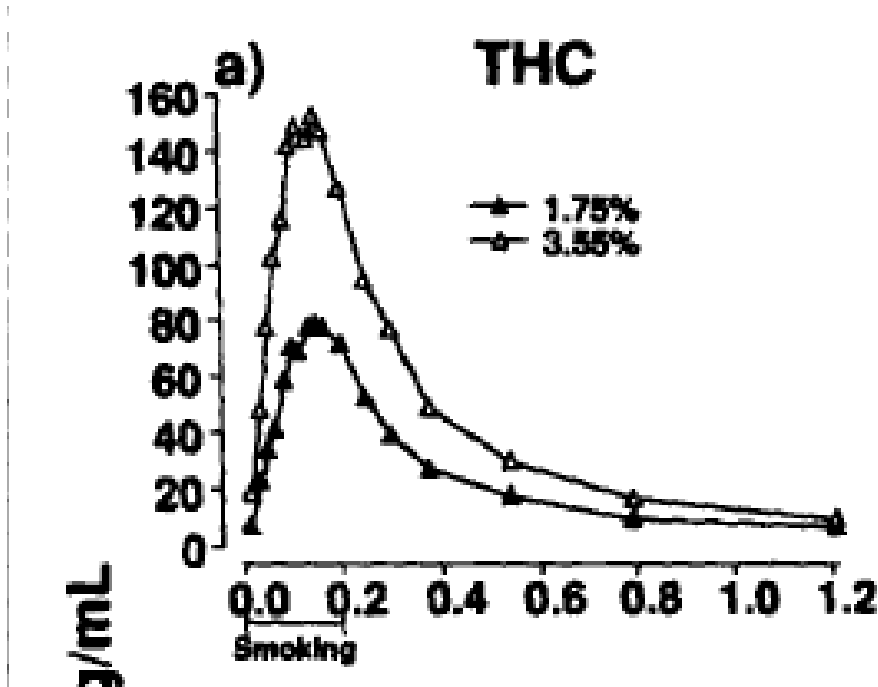
Figure 4. Whole blood mean THC after ingestion of 20 mg dronabinol or a milk hemp decoction containing 16.5 or 45.7 mg THC. From Menetrey et al 2005.(10)
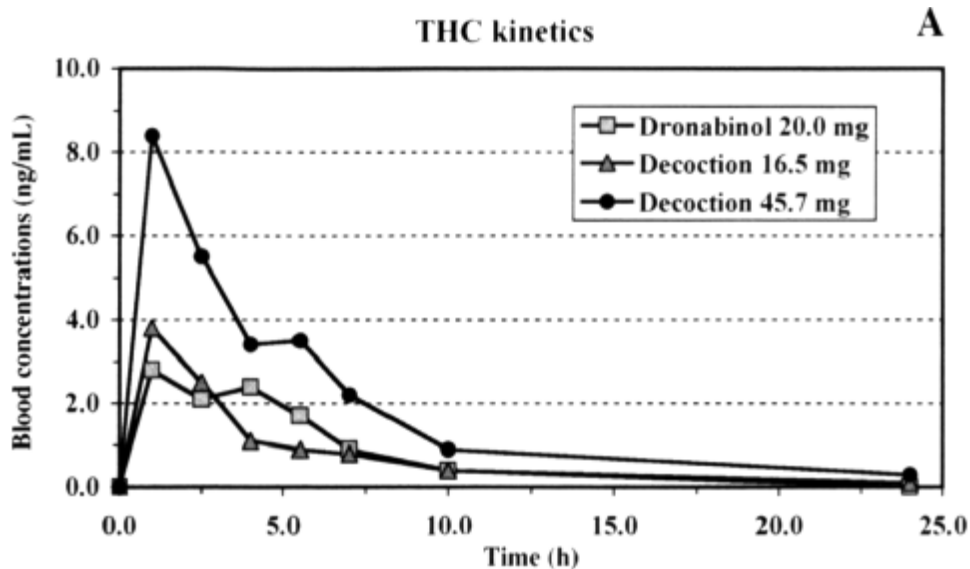
Figure 5. Mean plasma THC levels vs. time after oral THC doses of 0 (placebo) to 90 mg in 5 to 7 subjects. From Lile et al (2013).(34)
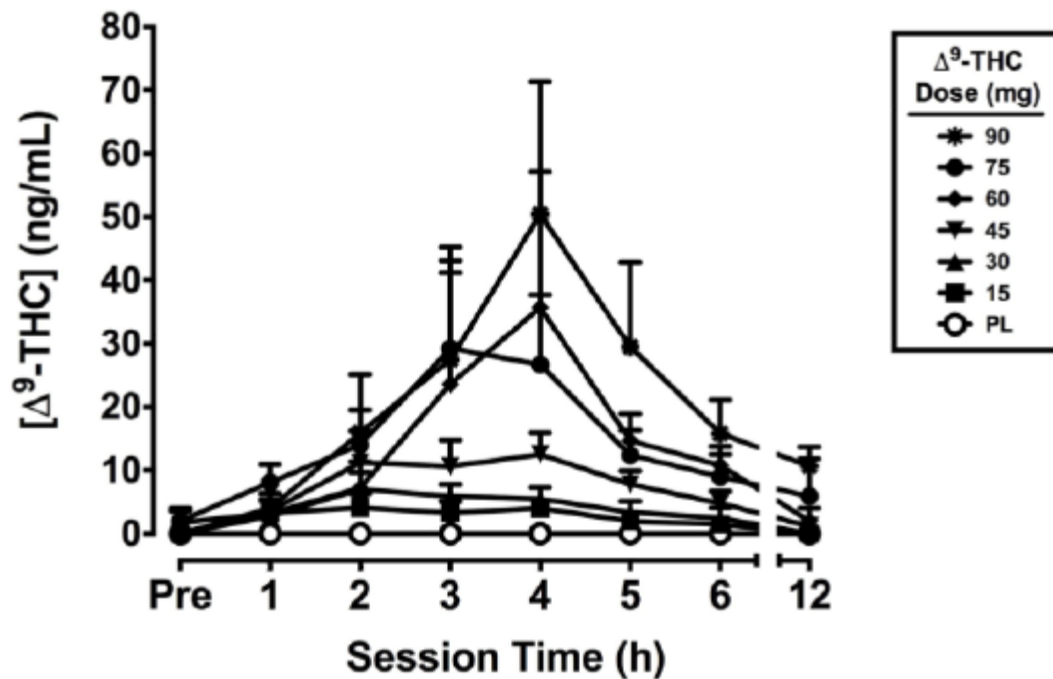
Figure 6. Individual subjects' peak plasma THC levels by dose (N=7). From Lile et al (2013).(34)
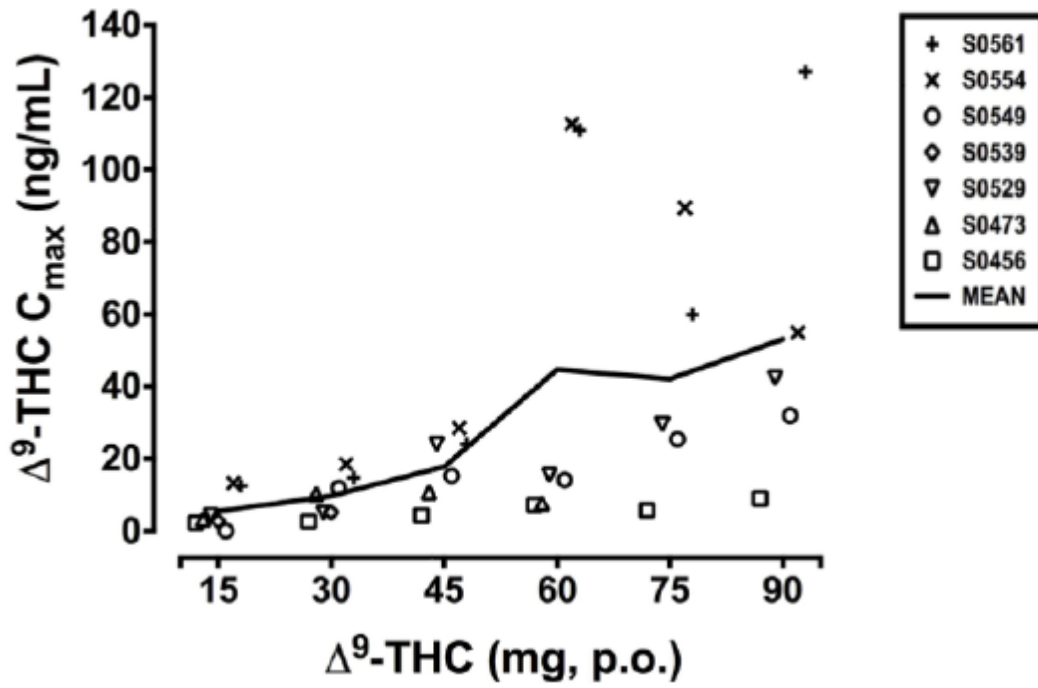
Figure 7. Plasma THC Concentration-Time Curves for vaporized and smoked marijuana by THC strength (means and 90% confidence intervals). From Abrams et al 2007.(12)
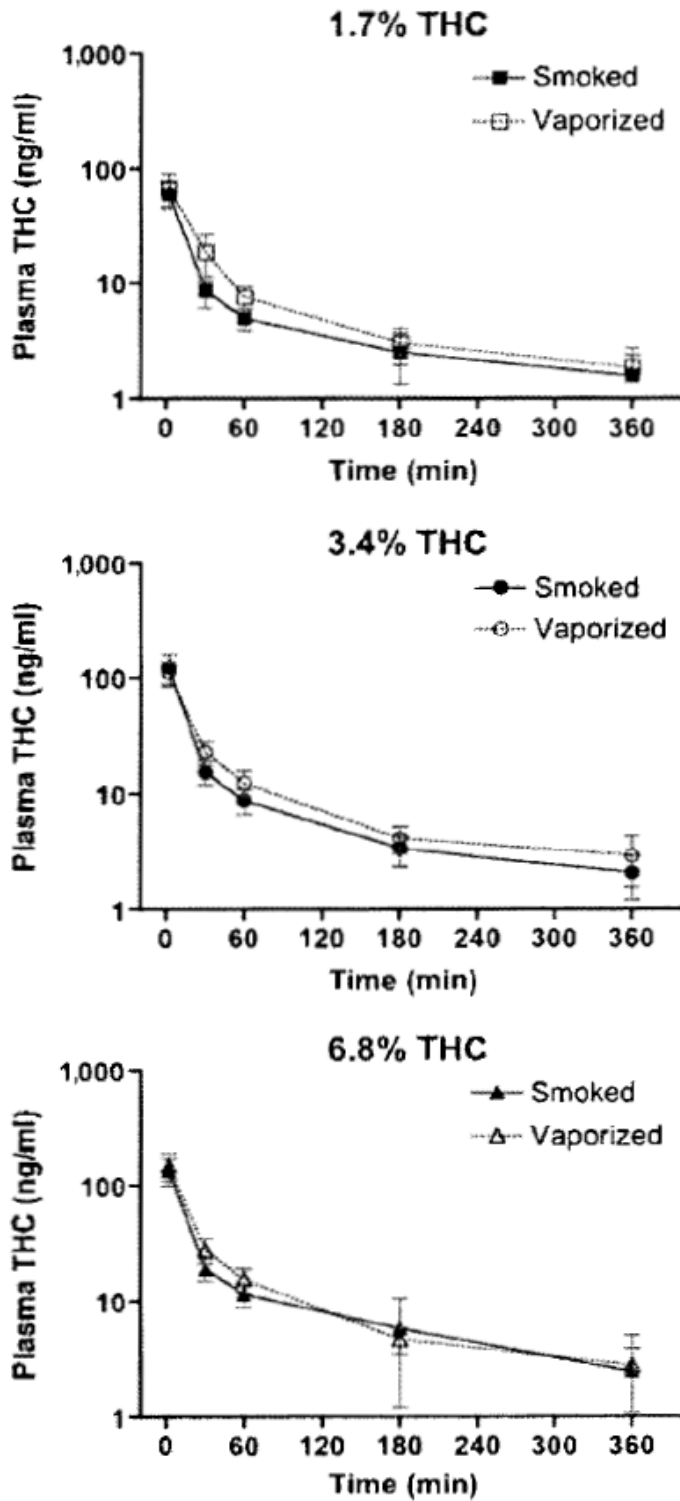
Figure 8. Performance vs. Time Since Smoking. The percentage of impaired performance test results was greatest in the first hour and decreased to < 15% (the cutoff for impairment) at a mean 4.75 hrs (range 3.75-5.75) post-use. From Berghaus et al 2011.(22)

THC smoking ≥9 - <18 mg, time-dependent impairment (44 studies, 317 effects)
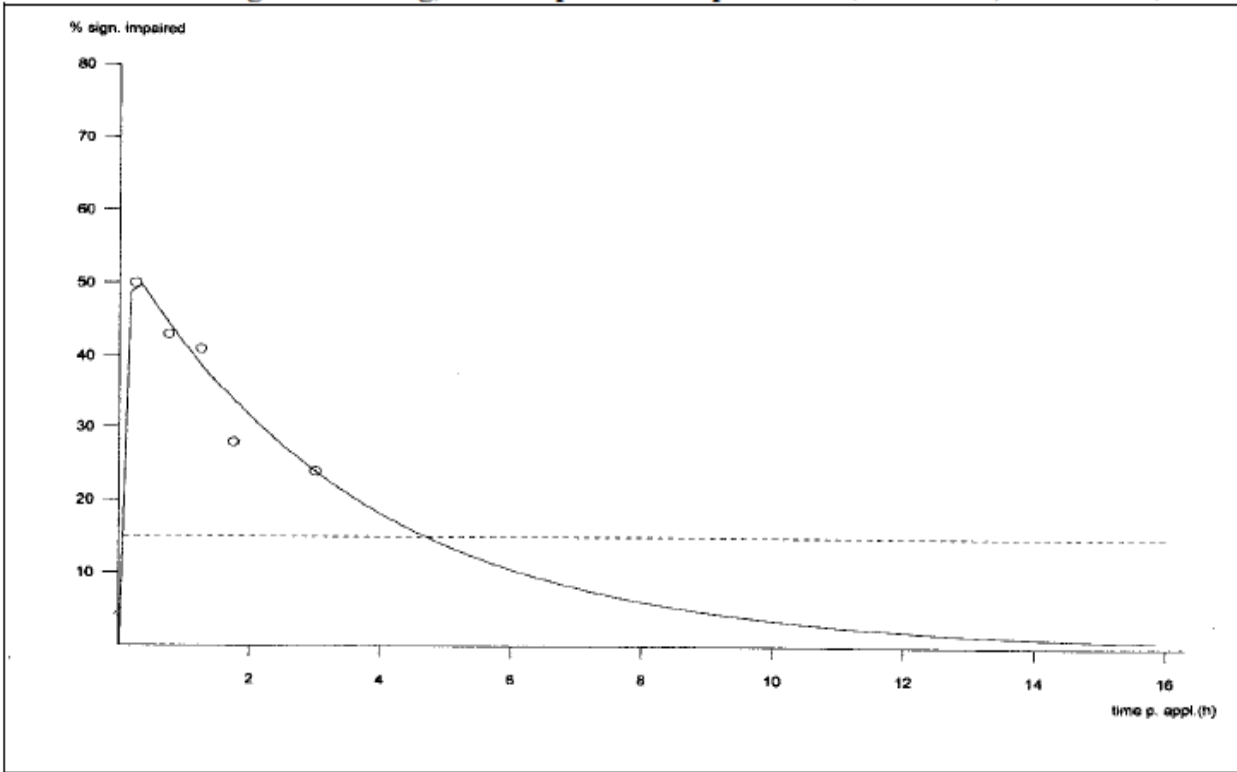
Figure 9. Mean (SE) values for compensatory response frequency (lamda-c) on critical tracking task (upper graph) and for percentage of correct detections (hits) and number of control losses on divided attention task (lower graphs) after 500 µg/kg THC or placebo. N=24. From Ramaekers et al 2009.(19)
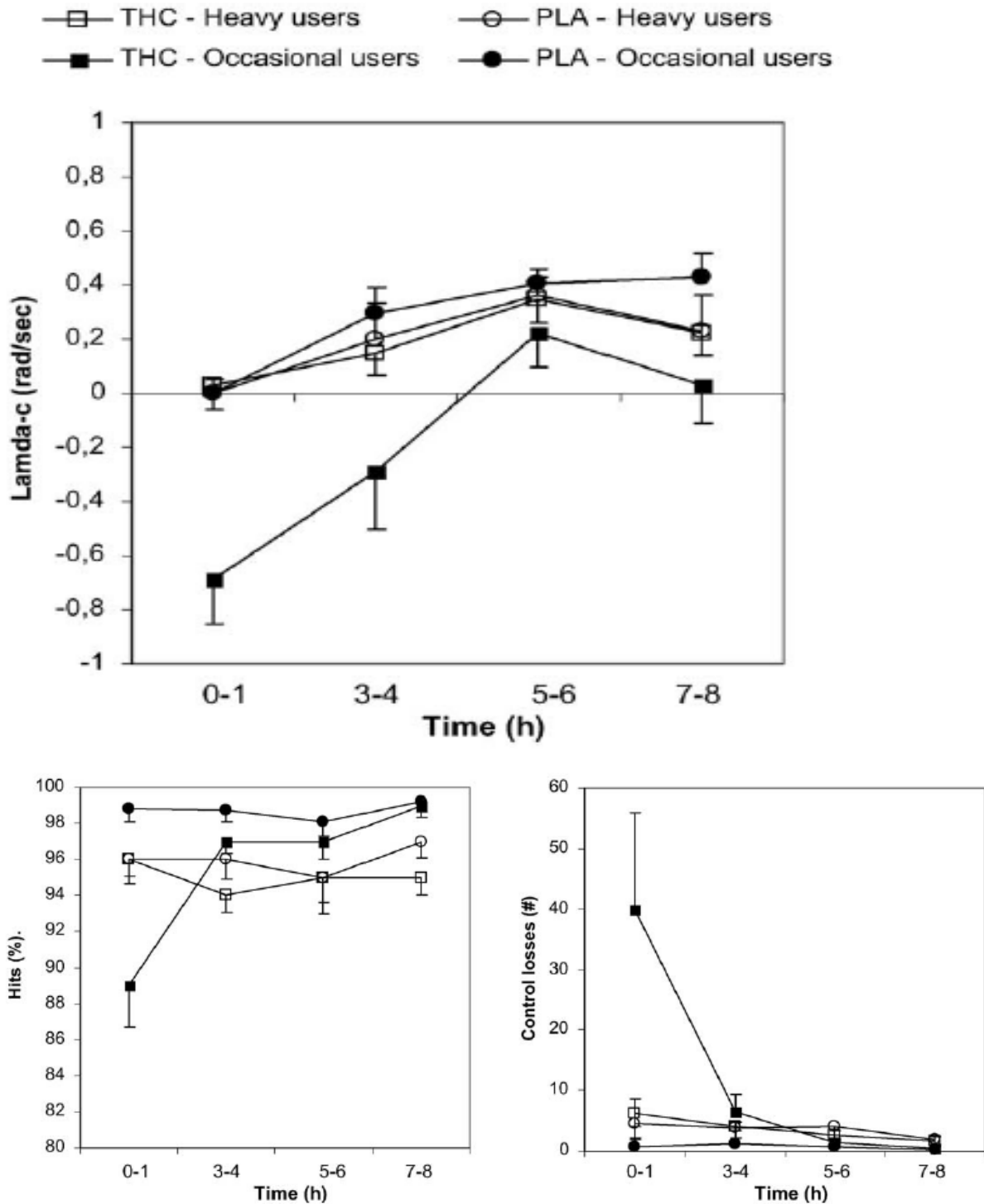
Figure 10. Performance vs. Time Since Oral Ingestion. The percentage of impaired performance test results was greatest in the first 1-2 hrs and decreased to < 15% (the cutoff for impairment) at a mean 5.0 hours (range 4.25-5.75) post-use. From Berghaus et al 2011.(22)

THC oral, ≥9 mg - <18 mg, time-dependent impairment (9 studies, 159 effects)
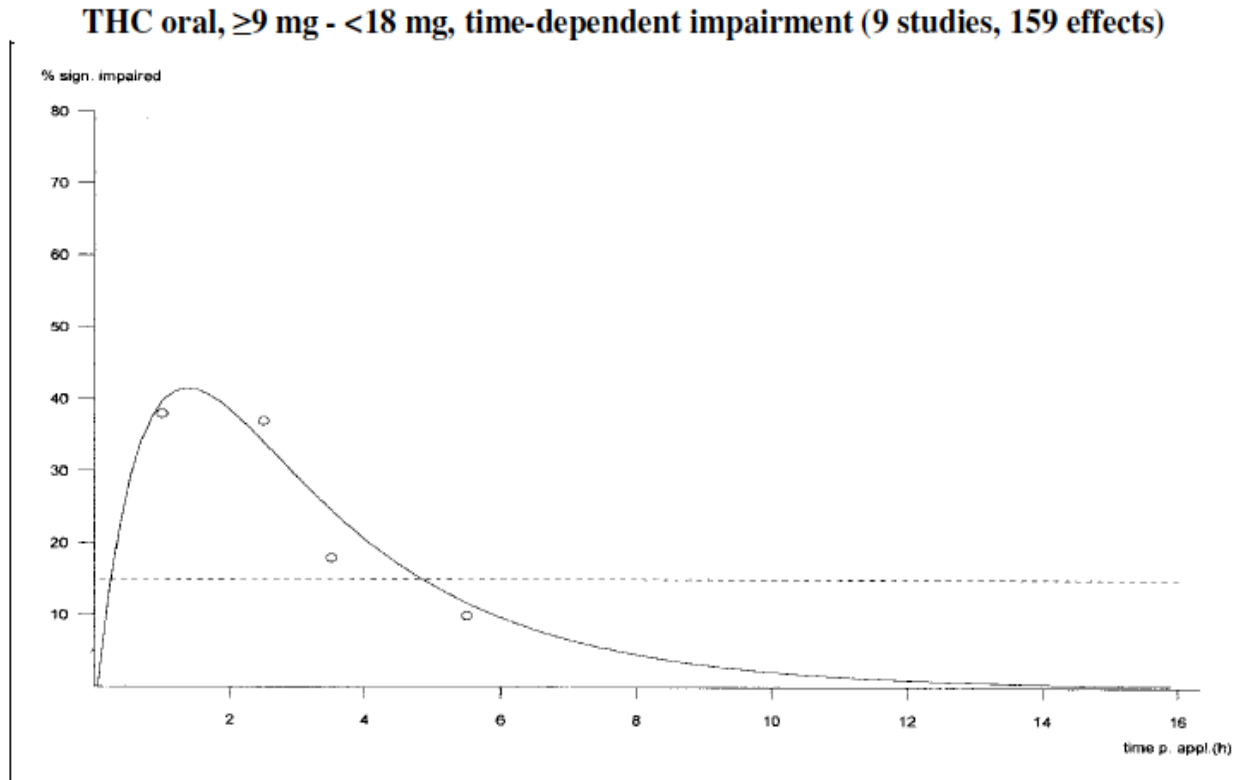
Figure 11. Mean results of tracking tests. Differences between all treatments vs. placebo and each treatment vs. placebo are statistically significant. Differences between treatments are not. Authors do not report at which time point each treatment becomes non-significantly different from placebo. N=8 (Menetrey 2005).(10)
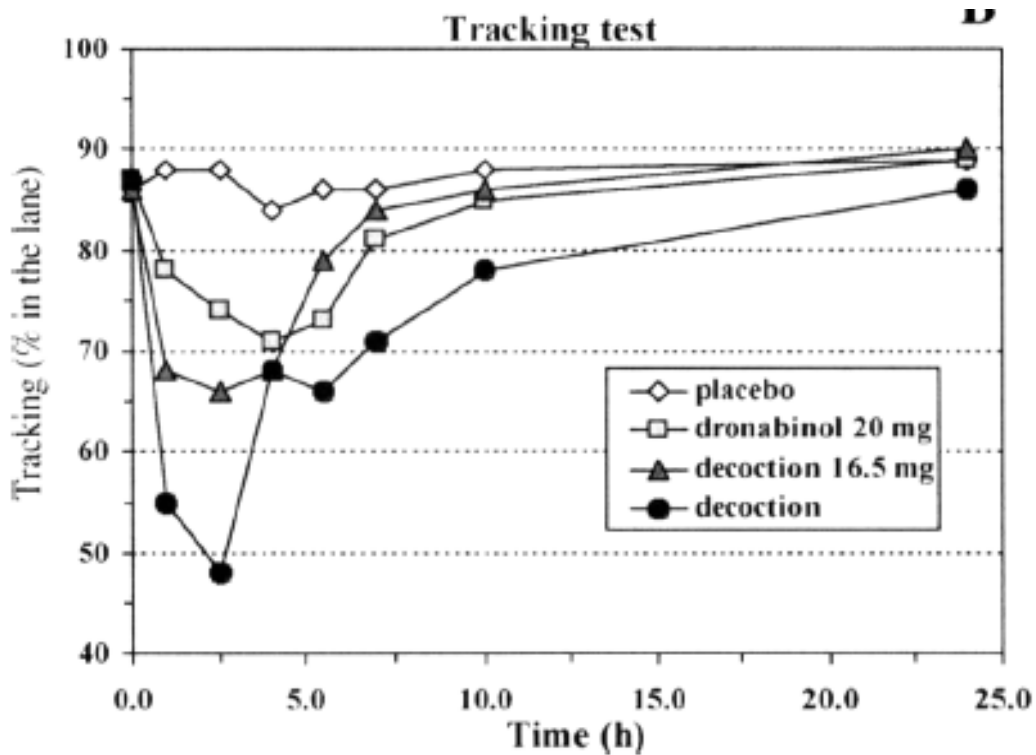
Figure 12. Time course for plasmaΔ9 -THC (left panel) and 11-OH-Δ9-THC (right panel) concentrations following administration of escalating doses of oral Δ9-THC. Data points represent means of 5–7 subjects. Uni-directional brackets indicate 1 SEM. The x-axis shows the time after dose in hours. "Pre" indicates the pre-dose measurement.
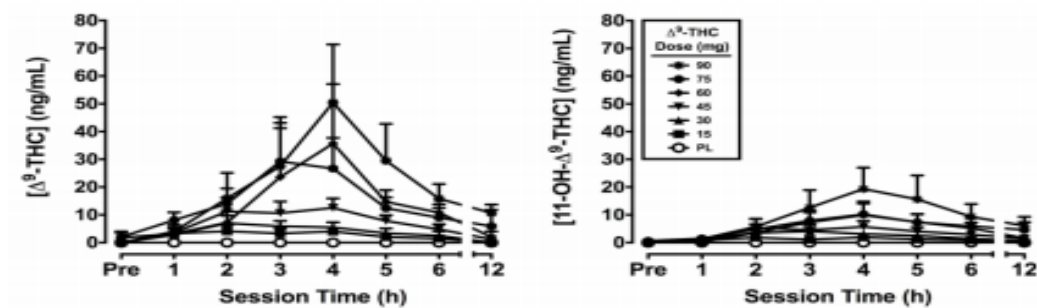
Table 3. Specific drug/drug classes with published clinical evidence of interactions with marijuana. Some drugs with published clinical evidence of a <u>lack</u> of interaction with marijuana are also included. These are marked with *.

Concomitant Drug/Drug Class	Description of Interaction	Contra-indicated	Increased THC Effect	Increased CNS Depres-sant Effect	Increased Concom-itant Drug Effect	Decreased Concom-itant Drug Effect	Type of Evidence	Reference
Chlorpromazine	Marijuana smoking increased clearance of chlorpromazine, as did tobacco smoking	No				Possible	Clinical study	(58)
Clozapine	Possible increased clozapine metabolism by marijuana induction of CYP1A2 (similar to tobacco). Therefore cessation may lead to increased clozapine levels and toxicity. Single case report of clozapine toxicity after tobacco and marijuana cessation	No			Possible (with marijuana cessation)	Possible	Case report	(59)
CNS depressants, e.g. alcohol, opioids, sedative-hypnotics, barbiturates, benzodiazepine, buspirone,	Additive drowsiness and CNS depression	No		Yes			Multiple clinical studies of marijuana and alcohol and a few with other CNS depressants	(5, 52, 55)

antihistamines, muscles relaxants, and many more								
Disulfiram	Possible hypomanic/ psychotic reaction	No	Possible				2 case reports	(52, 55)
Fluoxetine*	No change in fluoxetine efficacy and no serious adverse reactions in a 12 week clinical study of fluoxetine vs. placebo for marijuana-related depression	No					Small clinical study	(60)
Hexobarbital	May enhance CNS depressant effect. CBD decreased metabolism of hexabarbital but did not change its clinical effects.	No		Yes	Possible		Small clinical study	(61)
Hydrocortisone	THC increased serum cortisol, but effect is blunted in frequent users. Theoretical possibility of cushingoid syndrome	No			Possible		Clinical trial	(62)
Indinavir	Statistically significant decrease in peak	No				Possible	Randomized clinical trial	(63)

	concentration of indinavir with THC use						
Ketoconazole	Peak THC concentration was increased by 27%	No	Possible	Possible			Randomized clinical trial	(64)
MAO Inhibitors	Possible enhancement of orthostatic hypotension	No					Rationale that concomitant use of 2 agents that cause orthostatic hypotension will have an additive effect.	(55)
Nelfinavir*	No change in kinetic parameters.	No					Randomized clinical trial	(63)
Phenytoin	May enhance CNS depressant effect. In vitro, decreased phenytoin levels due to induction of metabolism by THC. Therefore, phenytoin levels may rise rapidly after THC cessation, causing toxicity. Intermittent THC use may cause transient subtherapeutic phenytoin levels. Case report of phenytoin toxicity	No		Yes	Possible (with marijuana cessation)	Possible	Multiple clinical studies of marijuana and alcohol and a few with other CNS depressants; in vitro study; case report	(55, 65, 66)

	after recreational use of phenytoin concomitantly with EtOH and marijuana.							
Theophylline	Smoked marijuana lowers theophylline concentrations, similar to tobacco. Unclear if only a smoking-related effect. No studies of oral marijuana/THC.	No				Possible	Two clinical studies	(67, 68)
Warfarin	Possible enhanced anticoagulant effect	No			Possible		Single case report of increased INR and bleeding, inconsistent with in vitro evidence of cannabis inducement of warfarin metabolism	(55, 69, 70)

Marijuana Use and Neurological, Cognitive and Mental Health Effects

Evidence Summary

COLORADO
Department of Public
Health & Environment

1. We found <u>substantial</u> evidence that adults who use marijuana heavily are more likely than non-users to have memory impairments for at least seven days after last using.

Heavy marijuana users had worse verbal learning and memory than non-users at baseline, at 1 day abstinence, and at 7 days abstinence (Pope 2001) High quality evidence based on strengths and limitations.
    Strengths:
- Longitudinal study following through 28 days of abstinence
- Demographically diverse
- 180 subjects, smallest group 45
- Studied current, former and non-user groups
- Users had used at least 5000 times lifetime
- 'Non-users' had to have used at least once, to reduce residual confounders
- Excluded other drug use, alcohol abuse, psychiatric disorders or medications, past head injury or other condition that may affect cognitive function
- Abstinence confirmed with daily urine tests
- Test administrators blinded to group status and in a different building
- Adjusted for age, gender, ethnicity, parental education, 1st degree relative substance abuse, and 1st degree relative psychiatric disorder
- Analysis done both with and without adjustment for verbal IQ score
- Secondary analysis adjusted for features of ADHD or conduct disorder
- Comparisons were all planned in advance, but because multiple tests were used, alpha was set at 0.01
- Effect size ranged from 6-24% lower score than non-users
    Minor limitations:
- Did not evaluate occasional users

Long-term dependent users, abstinent for 12 hours, had impaired verbal learning and less ability to avoid mental interference compared with controls or those who had used for a shorter period of time (Solowij 2002). Medium quality evidence based on strengths and limitations.
    Strengths:
- 135 subjects (33 controls)
- Broad adult range (19-65 yrs old)
- Subjects were excluded for psychotic disorder, dependence on alcohol or a non-marijuana drug, or any past injury or illness that may affect cognitive function
- 12 hour abstinence confirmed with urine tests
- Adjusted for IQ and age

- Effect size was 15-35% lower scores than control, across all parts of the Rey Auditory Verbal Learning Test (RAVLT)
- Despite the risk of multiple comparisons, scores were consistently lower among long-term users across all parts of the RAVLT(rather than sporadic differences more likely to be due to chance)

Minor limitations:
- Cross-sectional study
- Only recruited users who were seeking treatment- almost all of them met DSM criteria for marijuana dependence
- Not adjusted for alcohol use (despite exclusion for alcohol dependence)
- Over 100 comparisons are shown in the tables alone- Bonferroni correction was mentioned in the methods, but did not appear to be applied when reporting results

Amount of marijuana used is associated with worse performance in verbal memory, visual learning, executive functioning, psychomotor speed, complex reaction time and manual dexterity, even after 30 days abstinence (Bolla 2002) Medium quality evidence based on strengths and limitations.

Strengths:
- Marijuana use measured as joints per week, to better quantify the amount of use than other methods (group means were about 10, 40 & 90 joints per week)
- Results show a dose response
- Subjects excluded for drug or alcohol dependence other than marijuana, psychiatric disorder, neurological illness or trauma, or abnormal neurologic exam
- Subjects admitted for 30 days of monitored abstinence
- Examiner was blinded to subjects' group assignments
- Adjusted for age, gender, education, depression score and IQ

Minor limitations:
- Cross-sectional
- 22 subjects with varying amount of use, no controls
- 15 tests were performed, scores on 7 had a statistically significant negative correlation with amount of use, but the other 8 did not
- Not adjusted for alcohol use

Heavy marijuana users had worse performance on verbal learning and memory testing than 'normal' (Roebke 2014) Low quality evidence based on strengths and limitations.

Strengths:
- 131 subjects
- Mean performance among marijuana using group was more than 1.5 standard deviations below 'normal' performance
- Evidence of dose response - greater use (grams/day) correlated with worse scores

Major limitations:
- Sample is only marijuana users seeking treatment for marijuana
- No control group - comparison is to the 'normative sample' for the test used (hence, no adjustment could be done for any other variables)

Minor limitations:
- Cross-sectional
- No required abstinence - those with "obvious indications" of acute intoxication were excluded from testing

Recent marijuana users had worse scores than controls on multiple mental processes, including global performance, attention, working-memory, information processing, and executive function. (Thames 2014) Low quality evidence based on strengths and limitations.

Strengths:
- 158 subjects with over 40 in each group
- Adjusted for age, IQ and alcohol use
- Found increased effect (worse scores) with increased amount of marijuana used

Major limitation:
- Did not declare any abstinence period to avoid the acute effects of intoxication

Minor limitations:
- Cross-sectional study
- Did not declare an amount of marijuana use to qualify as a 'user' - presumably ANY vs. NONE
- Did not adjust for nicotine or any other drug use
- Effect size was not clearly given

Lifetime marijuana use and current marijuana use were each independently associated with
worse verbal and visual memory (Sanchez-Torres 2012) Low quality evidence based on strengths and limitations.

Strengths:
- Linear regressions were done on amount of lifetime use and amount of current use, instead of dividing into specific groups
- Adjusted for tobacco and IQ

Minor limitations:
- 42 subjects of interest, includes all levels of use for linear regression, so the number at any specific level is not clear (if the distribution is skewed, the linear regression may be less accurate for those in the middle of the range)
- Cross-sectional study
- Not adjusted for other drug or alcohol use
- Measuring for IQ was concurrent with other testing, so could lead to overcorrection

Marijuana use was associated with more episodes of forgetting in everyday and short-term memory. (Rodgers 2001) Low quality evidence based on strengths and limitations.

Strengths:
- 490 subjects
- Four use categories from none to 20+ times per month
- 40+ subjects in each group

Minor limitations:
- Only adjusted for ecstasy use
- Memory was assessed using an internet based memory questionnaire, not by formal testing

People who used marijuana monthly or more had worse decision making performance, but no significant difference in verbal memory, working-memory, processing speed, response inhibition or cognitive interference (Tamm 2013) Low quality evidence based on strengths and limitations.

Strengths:
- Users defined as monthly or more frequently, non-users as less than 4x in the past year
- Subjects excluded for other drug use monthly or more, or any binge drinking
- Adjusted for age, gender, IQ, race, alcohol, tobacco, maternal education

Major limitation:
- Non-ADHD subjects were not analyzed alone - the comparison between marijuana users and non-users were done with both ADHD and non-ADHD subjects included

Minor limitations:
- Matching was not used - subjects were selected from a larger study based on marijuana use and ADHD diagnosis
- Cross-sectional study
- Much variation in demographics between groups
- No complex tasks used
- Iowa Gambling Task might not reflect real-life decision making

2. We found substantial evidence that THC intoxication can cause acute psychotic symptoms, which are worse with higher doses.

THC acutely causes both positive and negative psychotic symptoms, as well as subjective and objective dissociative symptoms - all in a dose-dependent manner (D'Souza 2004) High quality evidence based on strengths and limitations.

Strengths:
- RCT, double-blind, cross-over design

- Excluded any DSM psychiatric or substance disorder, or any family history of major psychiatric disorder - confirmed self-report with interview of spouse or family member
- Subjects must have used marijuana at least once, but not have a cannabis use disorder
- Doses of 0, 2.5 and 5mg given to test dose effect
- Cross-over design used to measure within-subject changes by dose
- Different doses administered a week apart, with urine confirmation of abstinence throughout the study period and 2 weeks before
- Subjects refrained from caffeine and alcohol throughout the study period and 2 weeks before
- IV administration of THC to avoid differences in absorption
- Used the Positive and Negative Syndrome Scale, a validated measure of psychotic/schizophrenic symptoms that was developed to measure anti-psychotic medication effectiveness
- Used the Clinician Administered Dissociative States Scale, a validated measure of subjective and objective dissociative symptoms

Minor limitations:
- 18 subjects completed the three testing sessions
- 4 subjects dropped out
- Nicotine was not excluded
- Pure THC may have a different effect than natural marijuana with a mix of cannabinoids

THC acutely causes psychotic symptoms (Morrison 2009) Medium quality evidence based on strengths and limitations.

Strengths:
- RCT, double-blind, cross-over design
- Excluded any history of mental illness or substance dependence, currently screening positive for alcohol or drug dependence, severe medical disorders, or 1st degree relative with mental illness
- Cross-over design used to measure within-subject changes
- Cross-over sessions were 2 weeks apart
- Placebo controlled (0mg THC)
- IV administration of THC to avoid differences in absorption
- Abstained from alcohol or drugs 24 hrs prior to each session
- Used the Community Assessment of Psychic Experiences, a validated measure of psychotic symptoms in the general population
- Used the Positive and Negative Syndrome Scale, a validated measure of psychotic/schizophrenic symptoms that was developed to measure anti-psychotic medication effectiveness
- Used the UMACL (mood adjective checklist), a validated measure including arousal and sedation

Minor limitations:
- 19 subjects completed the two testing sessions

- 3 subjects dropped out
- All subjects were male
- One subject tested positive for marijuana at the beginning of both sessions
- Did not test different doses of THC
- Pure THC may have a different effect than natural marijuana with a mix of cannabinoids

THC acutely causes negative psychotic symptoms, which are not due to sedation (Morrison 2011) Medium quality evidence based on strengths and limitations.
  Strengths:
- RCT, double-blind, cross-over design
- Excluded any history of mental illness or substance dependence, currently screening positive for alcohol or drug dependence, severe medical disorders, or 1st degree relative with mental illness
- Cross-over design used to measure within-subject changes
- Cross-over sessions were 2 weeks apart
- Placebo controlled (0mg THC)
- IV administration of THC to avoid differences in absorption
- Abstained from alcohol or drugs 24 hrs prior to each session
- Used the Community Assessment of Psychic Experiences, a validated measure of psychotic symptoms in the general population
- Used the Positive and Negative Syndrome Scale, a validated measure of psychotic/schizophrenic symptoms, used to measure anti-psychotic medication effectiveness
- Used the UMACL (mood adjective checklist), a validated measure including arousal and sedation
  Minor limitations:
- 19 subjects completed the two testing sessions
- 3 subjects dropped out
- All subjects were male
- One subject tested positive for marijuana at the beginning of both sessions16
- Did not test different doses of THC
- Pure THC may have a different effect than natural marijuana with a mix of cannabinoids

3. We found <u>moderate</u> evidence that adults who use marijuana regularly are more likely than non-users to have symptoms or diagnosis of depression.

A meta-analysis concluded that regular marijuana users are more likely to have future depression than non-users (OR=1.62 CI 1.21-2.16), (Lev-Ran 2013) Medium quality evidence based on strengths and limitations.
  Strengths:

- Seven longitudinal studies were available that evaluated regular users
- Studies had to be longitudinal, with samples from the general population, be specific to cannabis use and to depression, and correct for or exclude depression at baseline
- Two types of sensitivity analysis were used to confirm the findings - limiting to studies of highest methodological quality, and limiting to studies with a diagnosis of depression
- No publication bias was found with both funnel plot analysis and Egger's regression-based test

Minor limitations:
- Effect size is relatively small and CI's come close to 1
- Both sensitivity analyses only had 4 studies available, had lower OR's than the full group, and had wide CI's just reaching or crossing one (OR 1.34 CI 0.96-1.87 and OR 1.43 CI 1.00-2.05)

Individuals with marijuana abuse or dependence are more likely to develop major depression than those without (OR=1.78 CI 1.17-2.71) (Pacek 2013) Medium quality evidence based on strengths and limitations.

Strengths:
- Over 34,000 subjects
- Longitudinal study with follow-up at 3 years
- 86.7% follow-up
- Diverse sample population representative of the general US population demographics
- Only counted incident depression (new at follow-up, not present at baseline)
- Adjusted for gender, age, marital status, race, education, income and family history of depression

Minor limitations:
- Only assessed those qualifying for marijuana abuse or dependence, based on DSM-IV
- Not assessed or adjusted for depressive indicators at baseline, only depression meeting diagnostic criteria

4. We found <u>limited</u> evidence that adults who use marijuana regularly are more likely than non-users to have impaired decision making for up to two days without use.

Heavy marijuana users did not learn from negative outcomes and change their choices to avoid them (Fridberg 2010) Low quality evidence based on strengths and limitations.

Strengths
- Clear distinction between groups - users were near-daily for 5 years and non-users had none in the last year and an average of 20 times lifetime
- 12 hours abstinence

- Real-life $50 prize for performing well was offered to strengthen subject motivation
- Used the Iowa Gambling Task, a validated test of choices around positive and negative outcomes

Minor limitations:
- Cross-sectional study
- Only 17 users and 15 control subjects
- Differences in age, education, alcohol use and tobacco use weren't significantly different between groups, so they weren't adjusted for
- IQ was different between groups and not adjusted for

People who used marijuana monthly or more had worse decision making performance, but no significant difference in verbal memory, working-memory, processing speed, response inhibition or cognitive interference (Tamm 2013). Low quality evidence based on strengths and limitations.

Strengths:
- Users defined as monthly or more frequently, non-users as less than 4x in the past year
- Subjects excluded for other drug use monthly or more, or any binge drinking
- Adjusted for age, gender, IQ, race, alcohol, tobacco, maternal education

Major limitation:
- Non-ADHD subjects were not analyzed alone - the comparison between marijuana users and non-users were done with both ADHD and non-ADHD subjects included

Minor limitations:
- Matching was not used - subjects were selected from a larger study based on marijuana use and ADHD diagnosis
- Cross-sectional study
- Much variation in demographics between groups
- No complex tasks used
- Iowa Gambling Task might not reflect real-life decision making

5. We found <u>limited</u> evidence that adults who use marijuana are more likely than non-users to have symptoms or diagnosis of anxiety.

A meta-analysis concluded that marijuana users are more likely to have anxiety than non-users (OR=1.24 CI 1.06-1.45), and that there is a temporal relationship, such that marijuana use predicts future anxiety (OR=1.28 CI 1.06-1.54) (Kedzior 2014) Medium quality evidence based on strengths and limitations.

Strengths:
- 31 studies in final analysis
- Studies had to have samples from the general population, and had to have control groups of healthy non-users

- Only used ORs that were adjusted for as many confounders as possible
- Sensitivity analysis (one-study removed analyses) was used to confirm no individual study skewed the findings
- Publication bias was deemed unlikely with both Fail-Safe N and funnel plot analysis
- Analysis included all users, not just heavier users

Minor limitations:
- Only 5 longitudinal studies were available to assess the temporal relationship
- Effect size is relatively small and CI's come close to 1
- Analysis could not separate out occasional users
- Studies did not have consistent definition of marijuana use nor of anxiety

6. We found <u>limited</u> evidence that adults who use marijuana are more likely than non-users to have symptoms or diagnosis of psychosis, and increasing likelihood with greater marijuana use.

Marijuana users were more likely to develop psychosis over the course of three years than non-users, with increasing likelihood based on greater marijuana use (vanOs 2002) Medium quality evidence based on strengths and limitations.

3-year incidence of psychosis   - 0.8% among non-users
                                 - 1.1% among occasional users
                                 - 5.6% among regular users
                                         - 8.6% among heavy users Strengths:
- Longitudinal study
- Multistage, stratified random sampling from the entire adult population of the Netherlands (ages 18-64)
- Large study - 7,076 subjects at baseline and 4,848 at 3-year follow-up
- Excluded residents of psychiatric hospitals or other institutions
- Users were divided into 4 groups for analysis
- Incident psychosis was the outcome - new occurrence between baseline and 3-year follow-up
- The Composite International Diagnostic Interview was used to identify psychosis

Minor limitations:
- 2,228 lost for follow-up
- Only 2 or 3 cases of psychosis in each user group
- Less than 1% prevalence of marijuana use among the sample

7. We found <u>mixed</u> evidence for whether or not adults who use marijuana are more likely than non-users to have impaired executive functioning, after not using for a short time.

Amount of marijuana used is associated with worse performance in verbal memory, visual learning, executive functioning, psychomotor speed, complex reaction time and manual dexterity, even after 30 days abstinence (Bolla 2002) Medium quality evidence based on strengths and limitations.

Strengths:
- Marijuana use measured as joints per week, to better quantify the amount of use than other methods (group means were about 10, 40 & 90)
- Results show a dose response
- Subjects excluded for drug or alcohol dependence other than marijuana, psychiatric disorder, neurological illness or trauma, or abnormal neurologic exam
- Subjects admitted for 30 days of monitored abstinence
- Examiner was blinded to subjects' group assignments
- Adjusted for age, gender, education, depression score and IQ

Minor limitations:
- Cross-sectional
- 22 subjects with varying amount of use, no controls
- 15 tests were performed, scores on 7 had a negative correlation with amount of use, but the other 8 did not
- Not adjusted for alcohol use

Recent marijuana users had worse scores than controls on multiple mental processes, including global performance, attention, working-memory, information processing, and executive function. (Thames 2014) Low quality evidence based on strengths and limitations.

Strengths:
- 158 subjects with over 40 in each group
- Adjusted for age, IQ and alcohol use
- Found increased effect (worse scores) with increased amount of marijuana used

Major limitation:
- Did not declare any abstinence period to avoid the acute effects of intoxication

Minor limitations:
- Cross-sectional study
- Did not declare an amount of marijuana use to qualify as a 'user' - presumably ANY vs. NONE
- Did not adjust for nicotine or any other drug use
- Effect size was not clearly given

Marijuana users, abstinent for 12 hours, had no significant differences in processing speed or executive functioning compared with controls (Solowij 2002) Medium quality evidence based on strengths and limitations.

Strengths:
- 135 subjects (33 controls)
- Broad adult age range (19-65 yrs old)
- Subjects were excluded for psychotic disorder, dependence on alcohol or non-marijuana drug, or any past injury or illness that may affect cognitive function
- 12 hour abstinence confirmed with urine tests
- Adjusted for IQ and age

Minor limitations:
- Cross-sectional study
- Only recruited users who were seeking treatment- almost all of them met DSM criteria for marijuana dependence
- Not adjusted for alcohol use

Lifetime marijuana use was associated with worse processing speed but no significant difference in other executive functions (Sanchez-Torres 2012) Low quality evidence based on strengths and limitations.

Strengths:
- Linear regression was done on amount of lifetime marijuana use, instead of dividing into groups
- Adjusted for tobacco use and IQ

Minor limitations:
- 42 subjects of interest, includes all levels of marijuana use for linear regression, so the number at any specific level is not clear
- Cross-sectional study
- Not adjusted for other drug or alcohol use
- Measuring for IQ was concurrent with other testing, so could lead to overcorrection
- Multiple post-hoc comparisons were made, with no declared adjustment, therefore for this review several findings with p>0.01 were not considered significant

8. We found <u>mixed</u> evidence for whether or not adults who use marijuana heavily are more likely than non-users to have impairment of memory or other cognitive functions for at least 28 days after last use.

Heavy marijuana users who had abstained for at least 28 days had no significant difference from non-users in attention, executive functions, visuospatial memory, or verbal learning & memory (Pope 2001) High quality evidence based on strengths and limitations.

Strengths:
- Longitudinal study following through 28 days of abstinence
- Demographically diverse
- 180 subjects, smallest group 45

- Studied current, former and non-user groups
- Users had used at least 5000 times lifetime
- 'Non-users' had to have used at least once, to reduce residual confounders
- Excluded other drug use, alcohol abuse, psychiatric disorders or medications, past head injury or other condition that may affect cognitive function
- Abstinence confirmed with daily urine tests
- Test administrators blinded to group status and in a different building
- Adjusted for age, gender, ethnicity, parental education, 1st degree relative substance abuse, and 1st degree relative psychiatric disorder
- Analysis done both with and without adjustment for verbal IQ score
- Secondary analysis adjusted for features of ADHD or conduct disorder
- Comparisons were all planned in advance, but because multiple tests were used, alpha was set at 0.01

Minor limitations:
- Every result reported for the current and former user groups at 28 days (10 tests & subtests) was worse than for the non-user group, though none reached statistical significance
- Low alpha might mask an actual effect (type II error)

Amount of marijuana used is associated with worse verbal memory, visual learning, executive functioning, psychomotor speed, complex reaction time and manual dexterity, even after 30 days abstinence (Bolla 2002) Medium quality evidence based on strengths and limitations.

Strengths:
- Marijuana use measured as joints per week, to better quantify the amount of use than other methods (group means were about 10, 40 & 90)
- Results show a dose response
- Subjects excluded for drug or alcohol dependence other than marijuana, psychiatric disorder, neurological illness or trauma, or abnormal neurologic exam
- Subjects admitted for 30 days of monitored abstinence
- Examiner was blinded to subjects' group assignments
- Adjusted for age, gender, education, depression score and IQ

Minor limitations:
- Cross-sectional
- 22 subjects with varying amount of use, no controls
- 15 tests were performed, scores on 7 had a negative correlation with amount of use, but the other 8 did not
- Not adjusted for alcohol use

Marijuana users abstinent at least 28 days had worse executive function than controls, but no significant difference in global performance, attention, working-memory, or

information processing. (Thames 2014) Low quality evidence based on strengths and limitations.

Strengths:
- 158 subjects with over 40 in each group
- Adjusted for age, IQ and alcohol use
- Included this group of users abstinent at least 28 days (called the 'remote use' group)

Minor limitations:
- Cross-sectional study
- Did not declare an amount of marijuana use to qualify as a 'user' - presumably ANY vs. NONE
- Did not adjust for nicotine or any other drug use
- Gave no information on the average length of abstinence for the 'remote use' group
- Effect size was not clearly given
- No complex tasks used
- Measuring for IQ was concurrent with other testing, so could lead to overcorrection

Prior heavy marijuana users who had abstained for at least 6 months did not have a significant decrease in working memory vs. controls. (Smith 2014) Low quality evidence based on strengths and limitations.

Strengths:
- Studied former heavy users
- Equal male & female
- Adjusted for nicotine use

Minor limitations:
- Cross-sectional study
- Only 10 marijuana users in the group of interest (44 control)
- Recruitment and eligibility was unclear
- Memory tasks were simpler than some studies
- Not adjusted for education, alcohol, other drug use, or other variables
- Results were not clearly conveyed

REFRENCES CITED

Becker, B., Wagner, D., Gouzoulis-Mayfrank, E., Spuentrup, E., & Daumann, J. (2010). The impact of early-onset cannabis use on functional brain correlates of working memory. Prog Neuropsychopharmacol Biol Psychiatry, 34(6), 837-845. doi: 10.1016/j.pnpbp.2010.03.032.

Bloomfield, M. A., Morgan, C. J., Egerton, A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. Biol Psychiatry, 75(6), 470-478. doi: 10.1016/j.biopsych.2013.05.027.

Bolla, K. I., Brown, K., Eldreth, D., Tate, K., & Cadet, J. L. (2002). Dose-related neurocognitive effects of marijuana use. Neurology, 59(9), 1337-1343.

Bossong, M. G., Jager, G., Bhattacharyya, S., & Allen, P. (2014). Acute and non-acute effects of cannabis on human memory function: a critical review of neuroimaging studies. Curr Pharm Des, 20(13), 2114-2125.

Boyce, A., & McArdle, P. (2008). Long-term effects of cannabis. Paediatrics and Child Health, 18(1), 37-41.

Cousijn, J., Wiers, R. W., Ridderinkhof, K. R., van den Brink, W., Veltman, D. J., Porrino, L. J., & Goudriaan, A. E. (2012).Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. Addict Biol, 18(6), 1013-1023. doi: 10.1111/j.1369-1600.2012.00498.x.

D'Souza, D. C., Perry, E., MacDougall, L., Ammerman, Y., Cooper, T., Wu, Y. T., . . . Krystal, J. H. (2004). The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology, 29(8), 1558-1572. doi: 10.1038/sj.npp.1300496.

Evren, C. (2011). Cognitive functions in patients with Cannabis use disorders. Dusunen Adam, 24(3),1-2.

Evren, C. (2011). Effect of cannabis use on cognitive functions. Klinik Psikofarmakoloji Bulteni, 21, S82-S83.

Filbey, F., & Yezhuvath, U. (2013). Functional connectivity in inhibitory control networks and severity of cannabis use disorder. Am J Drug Alcohol Abuse, 39(6), 382-391. doi: 10.3109/00952990.2013.841710

Fridberg, D. J., Queller, S., Ahn, W. Y., Kim, W., Bishara, A. J., Busemeyer, J. R., . . . Stout, J. C. (2010). Cognitive Mechanisms Underlying Risky Decision-Making in Chronic Cannabis Users. J Math Psychol, 54(1), 28-38. doi: 10.1016/j.jmp.2009.10.002.

Grover, S., & Basu, D. (2004). Cannabis and psychopathology : update 2004. Indian J Psychiatry, 46(4), 299-309.

Hall, W. (2009). The adverse health effects of cannabis use: what are they, and what are their implications for policy? Int J Drug Policy, 20(6), 458-466. doi: 10.1016/j.drugpo.2009.02.013.

Hall, W., & Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. Drug Test Anal, 6(1-2), 39-45. doi: 10.1002/dta.1506.

Kedzior, K. K., & Laeber, L. T. (2014). A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. BMC Psychiatry, 14(1), 136. doi: 10.1186/1471-244x-14-136.

Klugman, A., & Gruzelier, J. (2003). Chronic cognitive impairment in users of 'ecstasy' and cannabis. World Psychiatry, 2(3), 184-190.

Lev-Ran, S., Roerecke, M., Le Foll, B., George, T. P., McKenzie, K., & Rehm, J. (2014). The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med, 44(4), 797-810. doi: 10.1017/s0033291713001438.

Morrison, P. D., & Stone, J. M. (2011). Synthetic delta-9-tetrahydrocannabinol elicits schizophrenia-like negative symptoms which are distinct from sedation. Hum Psychopharmacol, 26(1), 77-80. doi:10.1002/hup.1166

Morrison, P. D., Zois, V., McKeown, D. A., Lee, T. D., Holt, D. W., Powell, J. F., . . . Murray, R. M. (2009). The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychol Med, 39(10), 1607-1616. doi: 10.1017/s0033291709005522.

Moussa, M. N., & Porrino, L. (2013). Moderate and heavy marijuana use: Differences in whole-brain functional network structure that underlie Iowa gambling task performance. Neuropsychopharmacology, 38, S194-S195.

Pacek, L. R., Martins, S. S., & Crum, R. M. (2013). The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: results from a national sample. J Affect Disord, 148(2-3), 188-195. doi: 10.1016/j.jad.2012.11.059.

Plecas, D., Diplock, J., & Garis, L. (2012). An updated review of the research on the risks and harms associated to the use of marijuana. Journal of Global Drug Policy and Practice, 6(3).

Pope, H. G., Jr., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun-Todd, D. (2001). Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry, 58(10), 909-915.

Pujol, J., Blanco-Hinojo, L., Batalla, A., Lopez-Sola, M., Harrison, B. J., Soriano-Mas, C., . . . Martin-Santos, R. (2014).

Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. J Psychiatr Res, 51, 68-78. doi: 10.1016/j.jpsychires.2013.12.008

Rodgers, J., Buchanan, T., Scholey, A. B., Heffernan, T. M., Ling, J., & Parrott, A. (2001). Differential effects of Ecstasy and

cannabis on self-reports of memory ability: a web-based study. Hum Psychopharmacol, 16(8), 619-625. doi: 10.1002/hup.345

Roebke, P. V., Vadhan, N. P., Brooks, D. J., & Levin, F. R. (2014). Verbal learning in marijuana users seeking treatment: a comparison between depressed and non-depressed samples. Am J Drug Alcohol Abuse, 40(4), 274-279. doi: 10.3109/00952990.2013.875551

Sanchez-Torres, A. M., Basterra, V., Rosa, A., Fananas, L., Zarzuela, A., Ibanez, B., . . . Cuesta, M. J. (2013). Lifetime cannabis use and cognition in patients with schizophrenia spectrum disorders and their unaffected siblings. European Archives of Psychiatry and Clinical Neuroscience, 263(8), 643-653.

Schoeler, T., & Bhattacharyya, S. (2013). The effect of cannabis use on memory function: an update. Subst Abuse Rehabil, 4, 11-27. doi: 10.2147/sar.s25869

Schoeler, T., Kambeitz, J., & Bhattacharyya, S. (2013). The effect of cannabis on memory function in users with and without a psychotic disorder: A meta-analysis. European Neuropsychopharmacology, 23, S216-S217.

Serafini, G., Pompili, M., Innamorati, M., Temple, E. C., Amore, M., Borgwardt, S., & Girardi, P. (2013). The Association between Cannabis Use, Mental Illness, and Suicidal Behavior: What is the Role of Hopelessness? Front Psychiatry, 4, 125. doi: 10.3389/fpsyt.2013.00125

Shrivastava, A., Johnston, M., & Tsuang, M. (2011). Cannabis use and cognitive dysfunction. Indian J Psychiatry, 53(3), 187-191.

Smith, M. J., Cobia, D. J., Wang, L., Alpert, K. I., Cronenwett, W. J., Goldman, M. B., . . . Csernansky, J. G. (2014). Cannabis-related working memory deficits and associated subcortical morphological differences in healthy individuals and schizophrenia subjects. Schizophr Bull, 40(2), 287-299. doi: 10.1093/schbul/sbt176.

Sneider, J. T., Mashhoon, Y., & Silveri, M. M. (2013). A Review of Magnetic Resonance Spectroscopy Studies in Marijuana using Adolescents and Adults. J Addict Res Ther, Suppl 4. doi: 10.4172/2155-6105.S4-010

Solowij, N. (1995). Do cognitive impairments recover following cessation of cannabis use? Life Sci, 56(23-24), 2119-2126.

Solowij, N., Stephens, R. S., Roffman, R. A., Babor, T., Kadden, R., Miller, M., . . . Vendetti, J. (2002). Cognitive functioning of long-term heavy cannabis users seeking treatment. Jama, 287(9), 1123-1131.

Tamm, L., Epstein, J. N., Lisdahl, K. M., Molina, B., Tapert, S., Hinshaw, S. P., . . . Swanson, J. M. (2013). Impact of ADHD and cannabis use on executive functioning in young adults. Drug Alcohol Depend, 133(2), 607-614. doi: 10.1016/j.drugalcdep.2013.08.001.

Thames, A. D., & Arbid, N. (2013). Acute and non-acute effects of cannabis on neurocognitive functioning. Neuropsychopharmacology, 38, S466-S467.

Thames, A. D., Arbid, N., & Sayegh, P. (2014). Cannabis use and neurocognitive functioning in a non-clinical sample of users. Addict Behav, 39(5), 994-999. doi: 10.1016/j.addbeh.2014.01.019.

van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol, 156(4), 319-327.

Volkow, N. D., Baler, R. D., Compton, W. M., & Weiss, S. R. (2014). Adverse health effects of marijuana use. N Engl Med, 370(23), 2219-2227. doi: 10.1056/NEJMra1402309.

Wilcox, H. C. (2004). Epidemiological evidence on the link between drug use and suicidal behaviors among adolescents. Can Child Adolesc Psychiatr Rev, 13(2), 27-30.

Marijuana Use and Respiratory Effects

Evidence Summary

COLORADO
Department of Public
Health & Environment

Definitions

Acute Use- Marijuana used within the last hour.
FEV1 : Forced Expiratory Volume in the first second.

FVC : Forced Vital Capacity: Total volume of air forcibly exhaled after maximal inhalation

FEV1/FVC Ratio: The proportion of lung vital capacity that can be exhaled in the first second of expiration - normal is >0.7

COPD – umbrella term for emphysema and chronic bronchitis

Emphysema – lung destruction and air trapping

Chronic Bronchitis - sputum production and cough

SGAW – airway conductance

RAW – airway resistance

EVIDENCE SUMMARY

1. We found <u>substantial</u> evidence that marijuana smoke, both mainstream and sidestream, contains many of the same cancer-causing chemicals as tobacco smoke.

- Analysis of mainstream smoke from 30 marijuana cigarettes (marijuana grown by Health Canada) and 30 tobacco cigarettes identified qualitatively similar types of chemicals including carbonyls, PAHs, and phenolic compounds (Moir 2008) *High quality finding*
- Smoke condensate from approximately 2000 marijuana (Mexican marijuana from National Institute of Mental Health) and tobacco cigarettes was analyzed by gas chromatography. Of the 153 total PAHs identified, 119 were identified in both marijuana and tobacco smoke. (Lee 1976) *Low quality finding*
- Smoke condensate from machine smoked Mexican marijuana was analyzed using HPLC and identified many of the same PAHs as are found in tobacco smoke (Sparacino 1990) *Low quality finding*
- Smoke from combusted marijuana (NIDA supplied, three 200 mg samples) was analyzed via GC/MS identified many of the same PAHs as are found in tobacco smoke (Gieringer 2004) *Low quality finding*

2. We found <u>limited</u> evidence from simulated smoking studies that smoke from water pipes or bongs contains more cancer-causing chemicals per milligram of THC compared to smoke from unfiltered joints.

Gowing 2000- Respiratory Harms of Smoked Cannabis.

- To determine the tar, CO, and THC content of smoke from cannabis and to consider factors that contribute to risks of respiratory harm.
- Compare typical (joint) smoke [75 cigarettes per sample] and smoke filtered through water pipe [eighty cones per sample].
- Cigarettes were tested following International Standards Organization (ISO) methods for the analysis of tobacco products:
  - 35mL puff volume
  - two second puff duration
  - 60 second interval between puffs
  - 23mm butt length
  - Cones did not stay lit in these conditions, puff duration increased to 6 seconds.
- Results
  - Tar and CO are increased when puff frequency is increased
  - Tar and CO are increased via a water pipe compared to unfiltered joint.
  - Tar and CO are increased by addition of tobacco to cannabis
- Discussion
  - Smoking conditions influence tar and CO deposition – length of breath-holding
  - *Low quality finding*

Gieringer D. 1999- Multidisciplinary Association for Psychedelic Studies (MAPS Newsletter
- Water pipes filter out more THC proportionately than other tars, this requires smokers to smoke more to reach the level of high they want.
- Water pipes may filter out non-solid gas phase toxins – hydrogen cyanide, carbon monoxide (MAPS Newletter 1993)
- Based on studies by Dr. Tashkin's group , pot smokers absorb four times as much tar in their lungs than cigarette smokers per weight smoked (Tashkin, *NEJM* 318: 347-51)
- Researchers tested seven sources for (1) total solid particles (2) THC, CDB, CBN
  - A regular rolled joint
  - Joint with a cigarette filter
  - Bong - standard
  - Bong – portable with folding stem
  - Bong – battery operated with motorized paddle to mix smoke and water
  - Vaporizer – battery powered metal hot plate in a jar (for smoke capture)
  - Vaporizer – hot air gun produced vapors, drawn through water.
- Results:
  - Unfiltered joint produced ratio of 1 part cannabinoids to 13 parts tar.

o   Water filtration is counterproductive, suggesting water absorbs THC more readily than the tar particulate.
o   Cigarette filter also performed worse.
o   Researchers propose any filtration system that picks up particulates is also likely to screen out cannabinoids due to their inherent stickiness
o   *Low quality finding*

3. We found <u>limited</u> evidence that smoking marijuana deposits more particulate matter per puff in the lungs compared to tobacco smoke.

- Puffs of marijuana were 70% larger, lasted 60% longer, were retained 4 times longer, and 35% more of the particulate matter was deposited as compared to tobacco puffs, but more puffs were taken from the tobacco cigarettes (Wu 1988) *Medium quality finding.*

Wu 1988, Pulmonary Hazards of Smoking Marijuana as Compared with Tobacco
- 15 combined tobacco and marijuana smokers, all had normal pulmonary function tests, all were otherwise healthy
- Subjects were measured while they smoked cigarette, then placebo marijuana, then marijuana. Subjects were asked to smoke in the usual way they would smoke each of those things. Had them smoke through a device that could filter part of cigarette (marijuana or tobacco) to measure what was inhaled and also hooked subject up to pneumotachygraph. Subjects exhaled into another filter to trap what came out
- Puffs of marijuana were 70% larger and lasted 60% longer than tobacco puffs, but more puffs were taken from the tobacco cigarette
- Mean inhaled volume was 36% larger and smoke retention time 4 times longer for marijuana
- With marijuana, subjects inhaled 2.8-3.3 times more insoluble particulate matter and had 32-35% more deposition of particulate in the respiratory tract. Combining these numbers resulted in 3.5 to 4.5 times greater tar burden
- Smoking marijuana caused fourfold greater increase in carboxyhemoglobin
- *Medium quality finding*

4. We found <u>substantial</u> evidence that marijuana use (inhaled or oral) results in an immediate short-term improvement of lung airflow.

- Marijuana reduced airflow resistance lasting up to one hour when smoked and 6 hours when taken orally in healthy subjects(Tashkin 1973) *Medium quality finding*
- Smoking marijuana during an acute attack of experimentally induced bronchoconstriction by methacholine or exercise resulted in complete and

sustained resolution of bronchoconstriction (Tashkin 1975) *Medium quality finding*
- Marijuana reduced airflow resistance lasting up to one hour when smoked and 6 hours when taken orally in asthmatics (Tashkin 1974) *Medium quality finding.*

Tashkin 1973 - Acute Pulmonary Physiologic Effects of Smoked Marijuana and Oral Delta-9-Tetrahydrocannabinol in Healthy Young Men
- 32 habitual (>3 joints/week) healthy marijuana smokers between ages 21-30 (2 week washout before study) and no tobacco for >6 mo. Underwent daily experiment for 36 days. There were no controls
- Smoked and oral THC in 2 concentrations each vs. placebo (0%THC marijuana) vs. tobacco (3 groups of 8 for smoked, 3 groups of 4 for oral)
- Significant dose response increase in heart rate noted in both forms
- Smoked marijuana increased specific airway conductance (50% increase in conductance, more than isoproterenol) in dose dependent manner compared to placebo, tobacco decreased conductance. Peak effect of 15 min and lasted up to one hour
- Oral marijuana increased airway conductance in dose dependent manner compared to placebo. Onset in one hour and lasting up to 6 hours
- *Medium quality finding*

Tashkin 1974, Acute effects of smoked marijuana and delta-9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects
- 10 subjects with stable asthma, otherwise healthy, 7 who had previously smoked marijuana previously but not heavily, none were tobacco smokers. Used double blind crossover design, with 2% THC vs. placebo for the smoked arm and 15mg oral THC vs. placebo for the oral arm. Spirometry, airway resistance, and conductance 10 min before and 10 min after isoproterenol used to compare response.
- Immediately after smoking marijuana SGaw increased 33-48% higher than baseline (P-value <0.05), similar in magnitude to isoproterenol, and lasted for at least 2 hours. There was no change with smoked placebo marijuana. Vtg (resistance) decreased slightly (4-13%), also significant at p<0.05.
- Oral studies showed peak 14-19% increase in Sgaw with onset at 1 hour that lasted 6 hours (p<0.5), no change in resistance noted. Overall no changes with placebo oral.
- *Medium quality finding*

  Tashkin 1975 - Effects of Smoked Marijuana in Experimentally Induced Asthma
- 8 subjects with bronchial asthma, subjects served as their own controls (each subject was own study comparing smoked marijuana to inhaled saline, inhaled isoproteronol, and placebo marijuana)
- Induced bronchospasm with exercise and also with methacholine in separate experiments to show that patients did meet definition of asthma

- Smoking marijuana during an acute attack of experimentally induced bronchoconstriction (by methacholine or exercise) resulted in complete and sustained resolution of bronchoconstriction
- *Medium quality finding*

5. We found <u>moderate </u>evidence that heavy marijuana smoking is associated with mild airflow obstruction.

- Chronic heavy marijuana smoking caused increased resistance and decreased conductance in a dose dependent manner (Tashkin 1987) *Low quality finding*
- Acute increase in FEV_1 seen immediately after smoking is not present in heavy daily smokers (Tashkin 1976) *Low quality finding*
- Heavy daily smoking for 47-59 days causes increased airway resistance and decreased conductance in a dose response manner (Tashkin 1976) *Medium quality finding*
- Marijuana smokers had decreased conductance and increased lung volumes on pulmonary function testing in a dose response relationship. (Aldington 2007) *Low quality finding*
- Marijuana smokers had higher lung volumes and airway resistance along with lower conductance over 14 years of follow up (Hancox 2010) *Medium quality finding*
- Indirect Evidence: Stopping smoking marijuana for one month can reverse increased airway resistance and decreased conductance (Tashkin 1976) *Medium quality finding*

Tashkin 1987, Respiratory Symptoms and Lung Function in Habitual Heavy Smokers of Marijuana Alone, Smokers of Marijuana and Tobacco, Smokers of Tobacco Alone, and Nonsmokers
- 279 heavy users (defined as using >10 joints per week for 5 years) 135 of which were also tobacco smokers, 97 nonsmokers, 70 tobacco only smokers
- Marijuana and combined smokers had more cough, wheeze, sputum production, and acute bronchitis episodes than non-smokers, but not more shortness of breath. Tobacco smokers and combined smokers were slightly worse.
- Marijuana smokers had higher airway resistance and lower specific conductance, measures of large airway function (as opposed to small airways)
- *Medium quality finding* for bronchitis symptoms
- *Low quality finding* for increased resistance and decreased conductance

Tashkin 1976, Subacute Effects of Heavy Marihuana Smoking on Pulmonary Function in Healthy Men
- 28 subjects age 21-33, smoked marijuana at least 4 days per week prior, 6 were tobacco smokers of ½ ppd or less.
- 94 day in-hospital experiment, 80 straight days of smoking as much marijuana as they wanted however no tobacco or other substances were allowed. Subjects served as their own controls. Pulmonary function tests were

measured periodically immediately after smoking and at 9AM, at least 9 hours after last ingestion
- Overall, subjects averaged 1.7 - 10 joints per day per subject
- FEV1 decreased slightly, airway resistance increased significantly, specific airway conductance decreased significantly, small decrease in diffusion capacity. However, nearly all subjects still had normal values, just different than their baseline.
- There was a dose response, the higher the average joints per day the greater the change in conductance and mid-expiratory flow rate. No dose response for FEV1 however
- All noted changes were reversed one month after discharge (though N=8 for this subset)
- Immediately after smoking, there was significant increase in FEV1 early in study, this effect disappeared as the study progressed
- *Medium quality finding* for heavy daily smoking for 47-59 days causing increased airway resistance and decreased conductance in a dose response manner
- *Medium quality finding* that stopping for one month can reverse these changes
- *Low quality finding* that acute increase in FEV1 seen immediately after smoking is not present in heavy daily smokers

Aldington, 2007. Effects of cannabis on pulmonary structure, function, and symptoms
- Convenience sample recruited from newspapers and radio. Defined marijuana use as greater than 5 joint-year. Study contained 4 groups: marijuana (75), marijuana/tobacco (91), tobacco (92), and non-smoker (81). Use reports were validated with urine cotinine and THC. Subjects underwent pulmonary function tests and high resolution CT.
- Marijuana use was associated with wheeze, chest tightness, cough, and chronic bronchitis. All odds ratios were <2
- Marijuana users had reduced FEV1:FVC ratio (borderline significance), decreased conductance, and increased TLC. Actual differences very small. There was a dose response relationship
- Marijuana users had higher percentage of low density lung tissue, but no evidence of emphysema. Only one had evidence of macroscopic emphysema and had major exposure (437 joint-year). Authors think decreased density related to air trapping and mild obstruction
- *Medium quality finding* for symptoms and decreased lung density.
- *Low quality finding* for obstruction

Hancox 2010, Effects of cannabis on lung function: a population-based cohort study
- Dunedin birth cohort, update at age 32. Only 40 cannabis only smokers with significant cannabis exposure. Full pulmonary function tests at this update vs.

previously only spirometry. Defined non-smokers of tobacco as less than 20 pack-years.
- Cannabis smokers had higher FVC, but no change in FEV1 or FEV1:FVC ratio. Higher TLC, FRC, and RV. Higher airway resistance and lower conductance.
- *Medium quality finding*

6. We found <u>mixed </u>evidence for whether or not smoking marijuana is associated with chronic obstructive pulmonary disease (COPD).

- Significant decrease in FEV1 seen in previous MJ smokers but not current smokers, though multiple different models over different study points analyzed to obtain this finding. Also significant decreases in FEV1/FVC in previous MJ smokers but not current (Sherrill 1991) *Low quality finding*
- No difference in the rate of decline of FEV_1 was seen in heavy marijuana smokers compared to non-smokers over an 8 year period (Tashkin 1997) *Medium quality finding*
- Marijuana smokers had higher lung volume (FVC) for all exposure levels (Pletcher 2012) *Medium quality finding*
- Marijuana smokers reported more wheeze and more episodes of acute bronchitis than non-smokers (Fligiel 1997) *Medium quality finding*
- Users of both tobacco and marijuana, but not marijuana alone, had significantly lower FEV_1/FVC over 8 years of follow up (Taylor 2002) *Low quality finding*
- No increased risk for COPD for marijuana only smokers, some increased risk noted for combined marijuana and tobacco smokers (Tan 2009) *Low quality finding*
- Marijuana smokers as compared to non-smokers had higher FEV_1 if <7 joint year exposure and equal FEV_1 at 7-10 joint years (Pletcher 2012) *Medium quality finding*
- Marijuana smokers had no change in FEV_1 or FEV_1/FVC (Hancox 2010) *Medium quality finding*

Sherrill 1991, Respiratory effects of non-tobacco cigarettes: A longitudinal study in general population
- Update of Tucson epidemiologic study. Observational only, no control for type of non-tobacco cigarette. Assumed to be mostly marijuana but not controlled for. 856 subjects between 20-60 (previously 15-40), only 79 current non-tobacco smokers (tobacco use among them was not reported) who smoked 7.9 joints/week initially but 4.0 joints/week at the end of the 7 years this study represents.
- Current non-tobacco smokers reported twice the amount of chronic cough, chronic phlegm, and wheezing than non-smokers (all p<0.05) in a dose response manner.
- Significant decrease in FEV1 of 142 ml (p<0.05) seen in previous marijuana smokers but not current marijuana smokers, though multiple different models

over different study points analyzed to obtain this finding. Also significant decreases in FEV1/FVC in previous marijuana smokers but not current.

- *Low quality finding*

Tashkin 1997, Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age

- Same Tashkin cohort. 144 heavy marijuana-only smokers (average 3.5 joints/day), 135 regular combined tobacco/marijuana smokers, 70 tobacco only, and 97 non-smokers initially enrolled, only 255 had more than one visit. Over 8 years, small reductions in use but most stayed the same
- No difference in rate of decline of FEV1 was seen in heavy marijuana smokers compared to non-smokers. Tobacco smokers did decline significantly faster, however combined marijuana/tobacco group decline was no different than non-smokers
- *Medium quality finding*

Pletcher 2012, Association between marijuana exposure and pulmonary function over 20 years

- Subset of CARDIA study. 5000 subjects with 20 years of follow-up. 69% retention at 20 years. Subjects underwent pulmonary function tests at 0, 2, 5, 10 , 20 years. 54% smoked either marijuana, tobacco, or both. 91 participants had no tobacco exposure and >10 joint-years. Average marijuana use was 2-3 episodes in last 30 days.
- Marijuana smokers as compared to non-smokers had higher FEV1 if <7 joint-year exposure, equal FEV1 at 7-10 joint-years, and non-significant small decline in FEV1 at greater than 10 joint-years. Higher FVC for all exposure levels
- *Medium quality finding*

Fligiel 1997, Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco

- Tashkin cohort. Performed bronchoscopy on 40 marijuana-only, 16 combined cocaine/marijuana, 44 combined marijuana/tobacco, and 53 nonsmokers (158 new subjects compared to 1987 study)
- No increase in cough, sputum, or shortness of breath. Marijuana smokers did have more wheeze and more episodes of acute bronchitis.
- No changes in any pulmonary function tests
- Increased histopathological features in all 11 precancerous categories, trend towards higher prevalence than tobacco only. There was an additive effect of marijuana and tobacco. No dose response could be shown.
- *Medium quality finding*

Taylor 2002. A Longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults

- Dunedin cohort. 26 year old follow up. 930 subjects.

- Trend towards worse FEV1:VC decrease with time, but this was not significant. Users with >900 lifetime uses had 1.33% lower ratio. Definite interaction with tobacco, this was significant meaning users of both had significantly worse ratio
- *Medium quality finding*

Tan 2009, Marijuana and chronic obstructive lung disease: a population-based study
- Subset of BOLD COPD study. Recruitment was by randomly calling 1000 people. Marijuana users were anyone who has ever used, substantial use defined as >50 lifetime uses. 856 completed spirometry and questionnaires, 124 were marijuana users (26 also tobacco), 86 were current marijuana users. Median lifetime marijuana use was 0.23 joint-years
- No increased risk for COPD or for respiratory symptoms for marijuana only smokers, however there was an increased risk for combined marijuana/tobacco smokers.
- *Low quality finding*

Hancox 2010, Effects of cannabis on lung function: a population-based cohort study
- Dunedin birth cohort, update at age 32. Only 40 cannabis only smokers with significant cannabis exposure. Full pulmonary function tests at this update vs. previously only spirometry. Defined non-smokers of tobacco as less than 20 pack-years.
- Cannabis smokers had higher FVC, but no change in FEV1 or FEV1:FVC ratio. Higher TLC, FRC, and RV. Higher airway resistance and lower conductance.
- *Medium quality finding*

7. We found <u>insufficient</u> evidence to suggest that marijuana smoking alone is associated with emphysema.

- Chronic heavy marijuana smoking (mean 5 joints per day) for 47-59 days was associated with a small decrease in diffusion of carbon monoxide, lower FEV1. These findings were reversible after 30 days cessation (Tashkin 1976) *Low quality finding*
- Marijuana users had higher percentage of low density lung tissue, but no evidence of macroscopic emphysema by CT scan (Aldington 2007) *Medium quality finding*

Tashkin 1976, Subacute Effects of Heavy Marihuana Smoking on Pulmonary Function in Healthy Men
- 28 subjects age 21-33, smoked marijuana at least 4 days per week prior, 6 were tobacco smokers of ½ ppd or less.
- 94 day in-hospital experiment, 80 straight days of smoking as much marijuana as they wanted however no tobacco or other substances were allowed. Subjects served as their own controls. Pulmonary function tests were

measured periodically immediately after smoking and at 9AM, at least 9 hours after last ingestion
- Overall, subjects averaged 1.7 - 10 joints per day per subject
- FEV1 decreased slightly, airway resistance increased significantly, specific airway conductance decreased significantly, small decrease in diffusion capacity. However, nearly all subjects still had normal values, just different than their baseline.
- There was a dose response, the higher the average joints per day the greater the change in conductance and mid-expiratory flow rate. No dose response for FEV1 however
- All noted changes were reversed one month after discharge (though N=8 for this subset)
- Immediately after smoking, there was significant increase in FEV1 early in study, this effect disappeared as the study progressed
- *Medium quality finding* for heavy daily smoking for 47-59 days causing increased airway resistance and decreased conductance in a dose response manner
- *Medium quality finding* that stopping for one month can reverse these changes
- *Low quality finding* that acute increase in FEV1 seen immediately after smoking is not present in heavy daily smokers

Aldington, 2007. Effects of cannabis on pulmonary structure, function, and symptoms
- Convenience sample recruited from newspapers and radio. Defined marijuana use as greater than 5 joint-year. Study contained 4 groups: marijuana (75), marijuana/tobacco (91), tobacco (92), and non-smoker (81). Use reports were validated with urine cotinine and THC. Subjects underwent pulmonary function tests and high resolution CT.
- Marijuana use was associated with wheeze, chest tightness, cough, and chronic bronchitis. All odds ratios were <2
- Marijuana users had reduced FEV1:FVC ratio (borderline significance), decreased conductance, and increased TLC. Actual differences very small. There was a dose response relationship
- Marijuana users had higher percentage of low density lung tissue, but no evidence of emphysema. Only one had evidence of macroscopic emphysema and had major exposure (437 joint-year). Authors think decreased density related to air trapping and mild obstruction
- *Medium quality finding* for symptoms and decreased lung density.
- *Low quality finding* for obstruction

8. We found <u>substantial</u> evidence that heavy marijuana smoking is associated with chronic bronchitis, including chronic cough, sputum production, and wheezing.

- Marijuana smokers had more cough, wheeze, sputum production, and acute episodes of bronchitis than non-smokers, but not more shortness of breath. This effect was additive when subjects also smoked tobacco (Tashkin 1987) *Medium quality finding* (Bloom 1987) *Low quality finding*
- Current non-tobacco smokers reported twice the amount of chronic cough, chronic phlegm, and wheezing than non-smokers (all p<0.05) in a dose response manner (Sherrill 1991) *Low quality finding*
- On bronchoscopy, the visual bronchitis index was higher in marijuana smokers than nonsmokers and comparable to tobacco smokers (8.2 and 8.0 compared to 4.4 in NS, 8.5 in combined marijuana and tobacco smokers) (Roth 1998) *Medium quality finding*
- Marijuana users were more likely than non-smokers to report wheezing apart from having a cold, exercise related shortness of breath, nocturnal awakening with chest tightness, and morning sputum production. Symptom prevalence was similar to smokers of 1-10 cigarettes per day. (Taylor 2000) *Low quality finding*
- Marijuana use was associated with chronic bronchitis, cough on most days, phlegm production, wheezing, and chest sounds without a cold. All odds ratios between 2 and 3. (Moore 2005) *Low quality finding*
- Marijuana use was associated with wheeze, chest tightness, cough, chronic bronchitis. All odds ratios were <2. (Aldington 2007) *Medium quality finding*

Tashkin 1987, Respiratory Symptoms and Lung Function in Habitual Heavy Smokers of Marijuana Alone, Smokers of Marijuana and Tobacco, Smokers of Tobacco Alone, and Nonsmokers
- 279 heavy users (defined as using >10 joints per week for 5 years) 135 of which were also tobacco smokers, 97 nonsmokers, 70 tobacco only smokers
- Marijuana and combined smokers had more cough, wheeze, sputum production, and acute bronchitis episodes than non-smokers, but not more shortness of breath. Tobacco smokers and combined smokers were slightly worse.
- Marijuana smokers had higher airway resistance and lower specific conductance, measures of large airway function (as opposed to small airways)
- *Medium quality finding* for bronchitis symptoms
- *Low quality finding* for increased resistance and decreased conductance

Bloom 1987, Respiratory Effects of Non-Tobacco Cigarettes
- Tucson epidemiologic study, observational only, no control for type of non-tobacco cigarette, assumed to be mostly marijuana but not controlled for. 136 subjects between 15-40 identified by random stratified cluster sample of Tucson households
- Current combined tobacco and marijuana smokers had more cough, phlegm, and wheeze than tobacco only smokers. Marijuana smokers compared to non-smokers had more of those same symptoms. The severity of symptoms was not reported.

- No change in pulmonary function tests noted but in unplanned subgroup, men who smoked marijuana had worse FEV1, Vmax, and FEV1:FVC ratio, tiny differences
- *Low quality finding*

Sherrill 1991, Respiratory effects of non-tobacco cigarettes: A longitudinal study in general population
- Update of Tucson epidemiologic study. Observational only, no control for type of non-tobacco cigarette. Assumed to be mostly marijuana but not controlled for. 856 subjects between 20-60 (previously 15-40), only 79 current non-tobacco smokers (tobacco use among them was not reported) who smoked 7.9 joints/week initially but 4.0 joints/week at the end of the 7 years this study represents.
- Current non-tobacco smokers reported twice the amount of chronic cough, chronic phlegm, and wheezing than non-smokers (all $p<0.05$) in a dose response manner.
- Significant decrease in FEV1 of 142 ml ($p<0.05$) seen in previous marijuana smokers but not current marijuana smokers, though multiple different models over different study points analyzed to obtain this finding. Also significant decreases in FEV1/FVC in previous marijuana smokers but not current.
- *Low quality finding*

Roth 1998, Airway inflammation in young marijuana and tobacco smokers
- Tashkin cohort. 40 subjects underwent bronchoscopy. Blinded videotapes of procedures were graded for erythema, edema, and airway secretions using modified visual bronchitis index. Also looked at biopsy specimens
- Trend towards more erythema in marijuana smokers but not significant (was significant in combined marijuana/tobacco smokers and in tobacco only smokers). There was increased edema in all smoking categories and mild increase in secretions in all smokers. Overall visual bronchitis index was higher in marijuana smokers compared to non-smokers and comparable to tobacco smokers (8.2 and 8.0 compared to 4.4 in non-smokers, 8.5 in combined marijuana/tobacco smokers)
- There was an increase in goblet cell hyperplasia, submucosal edema, and presence of inflammatory cells
- *Medium quality finding*

Taylor 2000, The respiratory effects of cannabis dependence in young adults
- Dunedin birth cohort, 1037 subjects. 91 were marijuana dependent (28 marijuana only smokers, 63 combined tobacco and marijuana) and 264 were tobacco only smokers. Mean use among marijuana dependent users was 230 times in the previous year. All were evaluated at age 21. Marijuana users used daily or near daily and screened positive for dependence
- Marijuana users more likely than non-smokers to report wheezing apart from having a cold, exercise related shortness of breath, nocturnal awakening with chest tightness, and morning sputum production

- Symptom prevalence among marijuana users was similar to smokers of 1-10 cigarettes per day
- Greater proportion of marijuana only users had FEV1:FVC ratio <80%, though there was no significant difference in the average ratio
- *Medium quality finding*

Moore, 2005. Respiratory effects of marijuana and tobacco use in a U.S. sample
- Used NHANES data. Defined use as >100 lifetime uses and at least once in the last month. 70% of marijuana smokers also smoked tobacco. Data was analyzed both controlling for this and without controlling.
- Marijuana associated with chronic bronchitis, cough on most days, phlegm, wheezing, and chest sounds without a cold. All odds ratios were between 2 and 3
- No increased risk for pneumonia, chest finding by a physician, or obstructive pulmonary function tests
- *Low quality finding*

Aldington, 2007. Effects of cannabis on pulmonary structure, function, and symptoms
- Convenience sample recruited from newspapers and radio. Defined marijuana use as greater than 5 joint-year. Study contained 4 groups: marijuana (75), marijuana/tobacco (91), tobacco (92), and non-smoker (81). Use reports were validated with urine cotinine and THC. Subjects underwent pulmonary function tests and high resolution CT.
- Marijuana use was associated with wheeze, chest tightness, cough, and chronic bronchitis. All odds ratios were <2
- Marijuana users had reduced FEV1:FVC ratio (borderline significance), decreased conductance, and increased TLC. Actual differences very small. There was a dose response relationship
- Marijuana users had higher percentage of low density lung tissue, but no evidence of emphysema. Only one had evidence of macroscopic emphysema and had major exposure (437 joint-year). Authors think decreased density related to air trapping and mild obstruction
- *Medium quality finding* for symptoms and decreased lung density.
- *Low quality finding* for obstruction

9. We found <u>limited </u>evidence that heavy marijuana smoking is associated with bullous lung disease.
- 4 heavy marijuana smokers had paraseptal apical distribution of large bullae with little parenchymal disease. Very unusual pattern. (Johnson 2000) *Low quality finding*
- 17 marijuana and tobacco smokers who had pneumothorax showed large unusual appearing apical bullae whereas 85 tobacco only smokers with pneumothorax showed small bullae (Beshay 2007) *Low quality finding*

- 10 heavy marijuana and tobacco smokers showed severe asymmetrical and variably sized bullae in apical and mid lung zones (Hii 2008) *Low quality finding*

Johnson 2000, Large lung bullae in marijuana smokers
- Case series of 4 patients, 2 were brothers. All smoked both marijuana and tobacco with an average of 26 pack-year tobacco smoking.
- Paraseptal apical distribution of large bullae, little parenchymal disease. Very unusual pattern for tobacco to cause
- *Low quality finding*

Beshay 2007, Emphysema and secondary pneumothorax in young adults smoking cannabis
- Chart review of 102 patients over 2 year period who presented with spontaneous pneumothorax. 17 heavy daily marijuana users (median 6 joints/day) also smoked tobacco (mean 7 pack-years) (group 1), 85 tobacco only smokers (group 2), 75 all-comers in another 2 year period (group 3). 12 in group 1 and 62 in group 2 had pulmonary function tests
- Marijuana and tobacco smokers showed large bullae and upper lobe predominant emphysema noted in all of group 1, only small bullae in group 2 and 3
- Group 1 had normal pulmonary function tests
- *Low quality finding*

Hii 2008, Bullous lung disease due to marijuana
- Case series of 10 patients, average age 40, who all smoked marijuana regularly for at least 12 months (average 74 joint-years). All were current or former tobacco smokers.
- Report severe asymmetrical and variably sized bullae in apical and mid lung zones
- *Low quality finding*

10. We found <u>insufficient</u> evidence to determine if smoking marijuana is associated with increased risk of respiratory infections.

- Marijuana smokers had a small increase in risk for respiratory visits, relative risk of 1.19 (CI 1.01-1.41) in those who smoked less than 10 years, but not for those that smoked more than 10 years (Pollen 1993) *Low quality finding*
- Marijuana smokers did not show any increased risk for pneumonia or for any finding on chest exam by a physician (Moore 2005) *Low quality finding*

Polen 1993, Health care use by frequent marijuana smokers who do not smoke tobacco
- Subjects were part of Kaiser Permanente health system and underwent Multiphasic health checkups where they answered questions. 452 daily marijuana users were matched to 450 controls by age, sex, race, and date of

first visit. No tobacco smokers were allowed. Marijuana users drank significantly more alcohol,
- Marijuana users reported more days ill with a cold, flu, or sore throat in the past year
- Small increase in risk for respiratory visits (regardless of eventual diagnosis), relative risk of 1.19 (CI 1.01-1.41). This was the only measure that held up after adjusting for alcohol consumption. This association was only present in those who smoked less than 10 years
- There was a non-significant increase in hospital admissions
- *Low quality finding*

Moore, 2005. Respiratory effects of marijuana and tobacco use in a U.S. sample
- Used NHANES data. Defined use as >100 lifetime uses and at least once in the last month. 70% of marijuana smokers also smoked tobacco. Data was analyzed both controlling for this and without controlling.
- Marijuana associated with chronic bronchitis, cough on most days, phlegm, wheezing, and chest sounds without a cold. All odds ratios were between 2 and 3
- No increased risk for pneumonia, chest finding by a physician, or obstructive pulmonary function tests
- *Low quality finding*

11. We found <u>substantial</u> evidence that heavy marijuana smoking is associated with pre-malignant lesions in the airway.

- Significant evidence of basal cell hyperplasia, squamous metaplasia, and goblet cell hyperplasia in marijuana smokers that was greater than tobacco smokers (Gong 1987) *Medium quality finding*
- Increased histopathologic features in all 11 precancerous categories with a nonsignificant trend towards higher prevalence than tobacco only. There was an additive effect of marijuana and tobacco, but no dose response could be shown. (Fligiel 1997) *Medium quality finding*
- Marijuana smokers had higher prevalence of basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, nuclear variation, increased mitotic figures, increased nuclear/cytoplasmic ratio, basement membrane thickening, subepithelial inflammation, and squamous cell metaplasia, and increased levels of EGFR and Ki-67, markers of lung cancer. All findings were as frequent or more frequent than tobacco smokers. There was a higher prevalence in combined marijuana and tobacco smokers (100% in many categories) (Barksy 1998) *Medium quality finding*

Gong 1987, Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco
- 39 subjects (subset of Tashkin's study) underwent bronchoscopy (16 marijuana only smokers (MS), 13 combined marijuana and tobacco smokers (MTS), 6 tobacco only smokers (TS), 4 non-smokers (NS)). Marijuana smokers had an

average of about 50 joint year smoking history. Biopsies were taken from carina and several deeper bronchial bifurcations
- Nearly all marijuana smokers had evidence of mild to moderate hyperemia (but limited erythema)
- *High quality finding* of basal cell hyperplasia, squamous metaplasia, and goblet cell hyperplasia. MS and MTS groups were greater than the TS group on these measures. MTS had more squamous metaplasia
- *Medium quality finding* for histopathological changes and hyperemia (though only 4 control subjects and was a convenience sample which could lead to recruiting people who are concerned about their lungs for some reason)

Fligiel 1997, Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco
- Tashkin cohort. Performed bronchoscopy on 40 marijuana-only, 16 combined cocaine/marijuana, 44 combined marijuana/tobacco, and 53 nonsmokers (158 new subjects compared to 1987 study)
- No increase in cough, sputum, or shortness of breath. Marijuana smokers did have more wheeze and more episodes of acute bronchitis.
- No changes in any pulmonary function tests
- Increased histopathological features in all 11 precancerous categories, trend towards higher prevalence than tobacco only. There was an additive effect of marijuana and tobacco. No dose response could be shown.
- *Medium quality finding*

Barksy 1998, Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco
- Also subset of Tashkin study. Bronchoscopy of 104 healthy volunteers, 28 non-smokers, 12 marijuana only smokers, 9 combined marijuana/tobacco smokers, 7 cocaine/marijuana, 9 cocaine/marijuana/tobacco. Average age of entire study was 39. Defined marijuana smokers as using 10 or more joints per week for 5 years or longer,
- Marijuana smokers had higher prevalence of basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, nuclear variation, increased mitotic figures, increased nuclear/cytoplasmic ratio, basement membrane thickening, subepithelial inflammation, and squamous cell metaplasia. All findings were as frequent as or more frequent than tobacco smokers. Even higher prevalence in combined marijuana/tobacco smokers (100% in many categories)
- Increased levels of EGFR and Ki-67 in marijuana only, worse in combined marijuana/tobacco
- *Medium quality finding* for precancerous markers (termed field cancerization effects)

12. We found <u>mixed</u> evidence for whether or not marijuana smoking is associated with lung cancer.

- Daily marijuana smokers had an odds ratio of 2.1 compared to non-smokers and 4.9 for those that smoked more than once per day (Zhang 1999) *Low quality finding*
- Marijuana smokers had odds ratio of 2.4 (CI 1.5-3.7) for lung cancer after adjustments for tobacco and occupational exposures. No dose response was noted. (Berthiller 2008) *Low quality finding*
- Any marijuana use was not associated with lung cancer however the highest tertile of use (>10.5 joint years) had relative risk of 5.7 (CI 1.5-21.6). Relative risk increased 8% for every joint yr of use, similar to the 7% increased risk for every pack year of cigarette smoking (Aldington 2008) *Low quality finding*
- Heavy marijuana use (>50 lifetime uses), but not any use, showed hazard ratio of 2.12 (CI 1.08-4.14) for lung cancer, no clear dose response relationship. (Callaghan 2013) *Low quality finding.*
- No significant association was seen between marijuana smoking and lung cancer (actually had trend towards less cancer with non-significant ORs less than 1). (Hashibe 2006) *Low quality finding*
- Pooled data from 6 separate studies showed odds ratio was 0.96 (CI 0.66-1.38) for habitual smokers compared to nonhabitual. Habitual smokers compared to never smokers odds ratio was 0.88 (CI 0.63-1.24). Odds ratio was 1.03 (0.54-1.98) for >20 yrs of use. Separate analysis restricted to 370 cases of never tobacco smokers showed similar results. (Zhang 2014) *Medium quality finding.*

Zhang 1999, Marijuana use and increased risk of squamous cell carcinoma of the head and neck
- Case control study of 173 subjects with new diagnosis squamous cell carcinoma of head and neck. 176 control subjects without cancer were recruited from blood donations. 91 had a mutagen sensitivity assay performed. Statistical analysis done with logistic regression analysis. Overall lifetime marijuana use was 13.9% in cases (22.9% in larynx and 19.2% in tongue), 9.7% in controls.
- Non-significant odds ratio (OR) for ever marijuana users, significant OR of 2.1 for those who smoked daily, and 4.9 for more than once per day. Nearly significant OR of 4.2 for those who smoked greater than 5 years.
- Stronger relationship in subjects under 55. No effect in subjects over 55
- Increased mutagen sensitivity in marijuana users, strong effect in combined smokers
- *Medium quality finding*

Berthiller 2008, Cannabis smoking and risk of lung cancer in men
- Pooled analysis of 3 case control studies. 430 cases of lung cancer compared to 778 controls in Tunisia, Morocco, and Algeria. 96% of cases were tobacco smokers compared to 68% of controls. Cases and controls came from same hospital; controls were admitted with something other than a tobacco related disease. Controls were matched on age and place of residence. Cannabis use

was defined as ever smoker or never smoker. Low exposure to cannabis overall (5 joints per month for 4 years in Tunisia, 9 joints/month in Algeria, not asked in Morocco). Only 3 cases and one control were current marijuana users.

- Odds ratio of 2.4 (CI 1.5-3.7) for lung cancer after adjustments for tobacco and occupational exposures. There was no dose response.
- *Low quality finding*

Aldington 2008, Cannabis use and risk of lung cancer: a case control study
- 79 cases of lung cancer identified from New Zealand Cancer Registry. 324 controls randomly selected from electoral roll, matched for 5 year age group. All age less than 55. Defined users as smoking >20 joints in lifetime
- Any cannabis use was not associated with lung cancer, however those in the highest tertile of use (>10.5 joint years) had relative risk of 5.7 (CI 1.5-21.6). Authors report a dose response with the relative risk increased 8% for every joint year of use, similar to the 7% increased risk for every pack year of cigarette use
- *Low quality finding*

Callaghan 2013, Marijuana use and risk of lung cancer: a 40-year cohort study
- Population based cohort of 49,321 18-20 year olds enrolled during military conscription in Sweden. Participants were tracked until 2009 through a multitude of Swedish databases. They were never reassessed, use was defined as what they reported on a non-anonymous survey at conscription into the military. Cannabis use was defined as ever used, heavy user defined as >50 lifetime uses. 91% of cannabis users also smoked tobacco. 189 incident lung cancers were found
- Heavy use (>50 lifetime uses), but not any use, showed hazard ratio of 2.12 (CI 1.08-4.14) for lung cancer.
- *Low quality finding*

Hashibe 2006, Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study
- Case-control design. Cases identified by Cancer Surveillance Program. Identified controls by asking neighbors of an identified case and matching for age and gender. 611 lung cancers, 303 oral, 90 laryngeal, and 108 esophageal.
- When controlling for tobacco and alcohol, no significant associations were seen (actually had trend towards less cancer with non-significant ORs less than 1). In smaller subset of never tobacco smokers, same findings.
- *Low quality finding*

Zhang 2014, Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium
- Data from 6 ILCCO studies that asked about cannabis were pooled together. Lifetime habitual use defined as 1 joint year. 2159 lung cancer cases compared to 2985 controls (controls identified through different methods in each study).

- Pooled odds ratio for lung cancer for all studies was 0.96 (CI 0.66-1.38). For habitual smokers compared to non-habitual or never smokers the odds ratio was 0.88 (CI0.63-1.24). The odds ratio was 1.03 (0.54-1.98) for those with >20 years of use.
- Separate analysis restricted to 370 cases of never tobacco smokers showed similar results
- *Medium quality finding*

13. We found <u>insufficient</u> evidence to determine if vaporizing marijuana is associated with respiratory health effects.

Gieringer D. 1999- Multidisciplinary Association for Psychedelic Studies (MAPS Newsletter
- Water pipes filter out more THC proportionately than other tars, this requires smokers to smoke more to reach the level of high they want.
- Water pipes may filter out non-solid gas phase toxins – hydrogen cyanide, carbon monoxide (MAPS Newletter 1993)
- Based on studies by Dr. Tashkin's group , pot smokers absorb four times as much tar in their lungs than cigarette smokers per weight smoked (Tashkin, *NEJM* 318: 347-51)
- Researchers tested seven sources for (1) total solid particles (2) THC, CDB, CBN
  o A regular rolled joint
  o Joint with a cigarette filter
  o Bong - standard
  o Bong – portable with folding stem
  o Bong – battery operated with motorized paddle to mix smoke and water
  o Vaporizer – battery powered metal hot plate in a jar (for smoke capture)
  o Vaporizer – hot air gun produced vapors, drawn through water.
- Results:
  o Unfiltered joint produced ratio of 1 part cannabinoids to 13 parts tar.
  o Water filtration is counterproductive, suggesting water absorbs THC more readily than the tar particulate.
  o Cigarette filter also performed worse.
  o Researchers propose any filtration system that picks up particulates is also likely to screen out cannabinoids due to their inherent stickiness
  o *Low quality finding*

References

1. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, et al. Cannabis use and risk of lung cancer: a case-control study. Eur Respir J. 2008;31(2):280-6.

2. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A, et al. Effects of cannabis on pulmonary structure, function and symptoms. Thorax. 2007;62(12):1058-63.

3. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. Am J Respir Crit Care Med. 1997;156(5):1606-13.

4. Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. J Natl Cancer Inst. 1998;90(16):1198-205.

5. Berthiller J, Straif K, Boniol M, Voirin N, Benhaim-Luzon V, Ayoub WB, et al. Cannabis smoking and risk of lung cancer in men: a pooled analysis of three studies in Maghreb. J Thorac Oncol. 2008;3(12):1398-403.

6. Beshay M, Kaiser H, Niedhart D, Reymond MA, Schmid RA. Emphysema and secondary pneumothorax in young adults smoking cannabis. Eur J Cardiothorac Surg. 2007;32(6):834-8.

7. Bloom JW, Kaltenborn WT, Paoletti P, Camilli A, Lebowitz MD. Respiratory effects of non-tobacco cigarettes. Br Med J (Clin Res Ed). 1987;295(6612):1516-8.

8. Callaghan RC, Allecbeck P, Sidorchuk A. Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control. 2013;24:1811-20.

9. Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. Chest. 1997;112(2):319-26.

10. Gates P, Jaffe A, Copeland J. Cannabis smoking and respiratory health: consideration of the literature. Respirology. 2014;19(5):655-62.

11. Gieringer D. Multidisciplinary Assocation for Pscheldelic Studies (MAPS) 1996 Newlsetter, Volume 6, Number 3. Revised. Nov. 1999.

12. Gieringer D, St. Laurent J, Goodrich S. Cannabis Vaporizer Combines Efficient Delivery of THC with Effective Suppression of Pyrolytic Compounds. Journal of Cannabis Therapeutics. 2004;4(1).

13. Gong H, Jr., Fligiel S, Tashkin DP, Barbers RG. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. Am Rev Respir Dis. 1987;136(1):142-9.

14. Gordon AJ, Conley JW, Gordon JM. Medical consequences of marijuana use: a review of current literature. Curr Psychiatry Rep. 2013;15(12):419.

15. Gowing LR, Ali RL, White JM. Respiratory harms of smoked cannabis. In: Australia DaASCS, editor. DASC Monograph No 8, Research Series2000.

16. Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR, McLachlan CR, et al. Effects of cannabis on lung function: a population-based cohort study. Eur Respir J. 2010;35(1):42-7.

17. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1829-34.

18. Hii SW, Tam JD, Thompson BR, Naughton MT. Bullous lung disease due to marijuana. Respirology. 2008;13(1):122-7.

19. Huber GL, Pochay VE, Pereira W, Shea JW, Hinds WC, First MW, et al. Marijuana, tetrahydrocannabinol, and pulmonary antibacterial defenses. Chest. 1980;77(3):403-10.

20. Johnson MK, Smith RP, Morrison D, Laszlo G, White RJ. Large lung bullae in marijuana smokers. Thorax. 2000;55(4):340-2.

21. Joshi M, Joshi A, Bartter T. Marijuana and lung diseases. Curr Opin Pulm Med. 2014;20(2):173-9.

22. Lee ML, Novotny M, Bartle KD. Gas chromatography/mass spectrometric and nuclear magnetic resonance spectrometric studies of carcinogenic polynuclear aromatic hydrocarbons in tobacco and marijuana smoke condensates. Anal Chem. 1976;48(2):405-16.

23. Maertens RM, White PA, Williams A, Yauk CL. A global toxicogenomic analysis investigating the mechanistic differences between tobacco and marijuana smoke condensates in vitro. Toxicology. 2013;308:60-73.

24. Moir D, Rickert WS, Levasseur G, Larose Y, Maertens R, White P, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol. 2008;21(2):494-502.

25. Moore BA, Augustson EM, Moser RP, Budney AJ. Respiratory effects of marijuana and tobacco use in a U.S. sample. J Gen Intern Med. 2005;20(1):33-7.

26. Owen KP, Sutter ME, Albertson TE. Marijuana: respiratory tract effects. Clin Rev Allergy Immunol. 2014;46(1):65-81.

27. Patel RB. Long-term Marijuana Use and Pulmonary Function. JAMA. 2012;307(17).

28. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012;307(2):173-81.

29. Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD. Health care use by frequent marijuana smokers who do not smoke tobacco. West J Med. 1993;158(6):596-601.

30. Roth MD, Arora A, Barsky SH, Kleerup EC, Simmons M, Tashkin DP. Airway inflammation in young marijuana and tobacco smokers. Am J Respir Crit Care Med. 1998;157(3 Pt 1):928-37.

31. Sherrill DL, Krzyzanowski M, Bloom JW, Lebowitz MD. Respiratory effects of non-tobacco cigarettes: a longitudinal study in general population. Int J Epidemiol. 1991;20(1):132-7.

32. Sparacino CM, Hyldburg PA, Hughes TJ. Chemical and Biological Analysis of Marijuana Smoke Condensate. In: Services USDoHaH, editor. 1990.

33. Tan WC, Lo C, Jong A, Xing L, Fitzgerald MJ, Vollmer WM, et al. Marijuana and chronic obstructive lung disease: a population-based study. CMAJ. 2009;180(8):814-20.

34. Tashkin DP. Increasing cannabis use: what we still need to know about its effects on the lung. Respirology. 2014;19(5):619-20.

35. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S, et al. Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis. 1987;135(1):209-16.

36. Tashkin DP, Shapiro BJ, Frank IM. Acute pulmonary physiologic effects of smoked marijuana and oral 9 -tetrahydrocannabinol in healthy young men. N Engl J Med. 1973;289(7):336-41.

37. Tashkin DP, Shapiro BJ, Frank IM. Acute effects of smoked marijuana and oral delta9-tetrahydrocannabinol on specific airway conductance in asthmatic subjects. Am Rev Respir Dis. 1974;109(4):420-8.

38. Tashkin DP, Shapiro BJ, Lee YE, Harper CE. Effects of smoked marijuana in experimentally induced asthma. Am Rev Respir Dis. 1975;112(3):377-86.

39. Tashkin DP, Shapiro BJ, Lee YE, Harper CE. Subacute effects of heavy marihuana smoking on pulmonary function in healthy men. N Engl J Med. 1976;294(3):125-9.

40. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. Am J Respir Crit Care Med. 1997;155(1):141-8.

41. Taylor DR, Fergusson DM, Milne BJ, Horwood LJ, Moffitt TE, Sears MR, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. Addiction. 2002;97(8):1055-61.

42. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR. The respiratory effects of cannabis dependence in young adults. Addiction. 2000;95(11):1669-77.

43. Tomar RS, Beaumont J, Hsieh JC. Evidence on the Carcinogenicity of Marijuana Smoke. In: Agency CEP, editor. 2009.

44. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.

45. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med. 1988;318(6):347-51.

46. Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, et al. Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium. Int J Cancer. 2014.

47. Zhang ZF, Morgenstern H, Spitz MR, Tashkin DP, Yu GP, Marshall JR, et al. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev. 1999;8(12):1071-8.

Marijuana Use and Extrapulmonary Effects

Evidence Summary

COLORADO
Department of Public
Health & Environment

Extra-pulmonary Disease: Research Questions and Findings

For Consideration by the Colorado Department of Public Health and the Environment Retail Marijuana Public Health Advisory Committee

Ashley Brooks Russell, PhD, MPH, Katelyn Hall, MPH, Lisa Barker, Madeline Morris
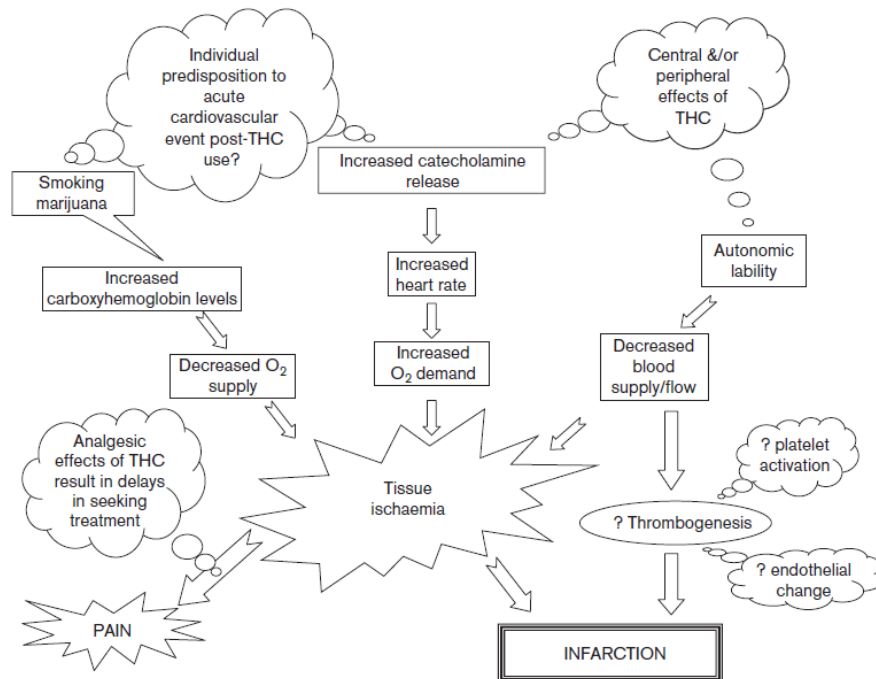
October 20th, 2014

DEFINITIONS AND GENERAL REMARKS:

USE DEFINITIONS:
        Heavy – daily or near daily use
        Regular – weekly or more often
        Occasional – less than weekly

Putative pathophysiological effects of following marijuana ingestion that may contribute to acute cardiovascular events (see text for details).

David G.E. Caldicotta, James Holmesa, Kurt C. Roberts-Thomsonb and Leo Mahar Keep off the grass: marijuana use and acute cardiovascular events, European Journal of Emergency Medicine 2005, 12:236–244.

Are marijuana users at a higher risk of heart attack?

SUMMARY STATEMENT 1: We found <u>limited evidence</u> that acute marijuana use increases risk of myocardial infarction.

> <u>Supporting Evidence:</u>
> 1 medium quality finding (Mittleman et al., 2001)
> - (a)   Conducted at 64 community and tertiary medical centers in the United States that were part of the Determinants of Myocardial Infarction Onset Study (The Onset Study) – authors conducted analysis at the Institute for the Prevention of Cardiovacscular Disease, Harvard Medical School, Boston, MA, USA
> - (b)   A case-crossover study that analyzes the timing of marijuana use prior to myocardial infarction in 3,882 individuals with a recent myocardial infarction.
> - (c)   94% male, mean age 43.7 +/- 8.0 years
> - (d)   Marijuana use was reported by only 124 patients (3.9%) and 9 patients reported use in the hour prior to onset of symptoms (0.2%).. Within one hour after smoking MJ, the risk of MI onset was elevated 4.8 fold (95% CI; 1.4-7.3) compared to periods of non-use. In the second hour post use, RR 1.7 (95%CI; 0.6-5.1) (e)   See Appendix A "Proposed Physiologic Effects of Cannabis on the Cardiovascular system
> "

> 1 low quality finding (Jouanjus et al., 2014)
> - (a)   Conducted by The French Association of the Regional Abuse and Dependence Monitoring Centres ((CEIP-A) Working Group on Cannabis Complications. Toulouse, France
> - (b)   A case-series from 2006 to 2010 that identifies 35 individuals with cardiovascular complications related to marijuana use. The mean age was 34.3 +/- 8.8 years with 86% of participants being male.
> - (c)   Medical data were abstracted including cardiovascular complications. There were 22 cardiovascular complications (20 acute coronary syndromes), 10 peripheral complications, and 3 cerebral complications. In 9 cases, the event led to the patient's death.
> - (d)   This information is gathered from the French Addictovigilance Network, they estimate that only 5% of adverse drug reactions are appropriately reported through this mechanism and the true incidence of cardiovascular complications in marijuana users is higher than reported here.
> - (e)   Twenty-one patients (60%) were identified as concomitant smokers, of whom six had personal cardiovascular history. No data on cotinine was presented.
> - (e)   Additional limitations result from inconsistent data collection during acute event. Many individuals in this case series were poly-users and or tobacco smokers, and no attempt was made to link acute use with severity of outcome.
> - (f)   See Appendix A "Proposed Physiologic Effects of Cannabis on the Cardiovascular system
> "

SUMMARY STATEMENT 2: We found insufficient evidence that acute marijuana use increases risk of death related to myocardial infarction/cardiovascular event.

    Supporting Evidence:
  1 low quality finding (Mukamal et al., 2008)
- (a)   Conducted at 45 community and tertiary medical centers in the United States that were part of the Determinants of Myocardial Infarction Onset Study (The Onset Study) – author's affiliation is Beth Deaconess Medical Center, Boston, MA, USA
- (b)   An inception (prospective) cohort study of 1,913 adults hospitalized with MI.
- (c)   Followed for 5 years with the median follow-up 3.8 years for cardiovascular mortality.
- (d)   The risk of death from a cardiovascular event was 2.5 times higher among less than weekly marijuana use compared with nonuse, though not significant (HR=2.5, 95% CI: 0.9-7.3). The risk of death from a cardiovascular event was 4.2 times higher among those that use marijuana weekly compared to no use (HR=4.2, 95% CI: 1.2-14.3).
- (e)   In age and sex adjusted models, the risk of cardiovascular morality was 1.9 times higher for any marijuana use (HR=1.9, 95% CI: 0.6-6.3) and for non-cardiovascular mortality was 4.9 times higher for any marijuana use compared to no marijuana use (HR=4.9, 95%CI: 1.6-14.7).
- (f)   In a comparison of survival distributions (log-rank test) of 42 marijuana users and 42 other patients matched on propensity score, there was difference between six deaths among marijuana users and one death among non-users (*p*=0.06).
- (g)   See Appendix A "Proposed Physiologic Effects of Cannabis on the Cardiovascular system "

    Supportive Evidence:
1 low quality finding (Frost et al., 2013)
- a)   Conducted at 64 community and tertiary medical centers in the United States that were part of the Determinants of Myocardial Infarction Onset Study (The Onset Study) – authors affiliation is the Cardiovascular Epidemiology Research Unit, Department of Medicine, Beth Deaconess Medical Center, Boston, MA, USA
- (a)   An inception (prospective) cohort study of 3,900 survivors of a myocardial infarction (MI) who were followed for 18 years for mortality with a median of 3.8 years of follow-up time.
- (b)   There were 22 deaths among the 109 who reported using marijuana at some time during the year before their MI. This death rate was 29% (95% CI: 0.81-2.85, *p*=0.28) higher than the death rate among those who did not report marijuana use, though it was not a statistically significant increase.
- (e)   See Appendix A "Proposed Physiologic Effects of Cannabis on the Cardiovascular system

Are marijuana users at a higher risk of stroke (ischemic stroke)?

Ischemic Stroke: The physical blockage of blood flow to an area of the brain, causing brain cells in the area to die. Ischemic strokes cause permanent brain damage and long term impairments

SUMMARY STATEMENT 3: We found limited evidence marijuana use increases risk of an ischemic stroke.

Supporting Evidence:
1 low quality finding (Wolff et al., 2011)
- (a)   Conducted by the Vascular Neurology Unit, University of Strasbourg Hospital, France
- (b)   A prospective case-series of 48 consecutive young (<45 years) patients admitted to the stroke unit with ischemic stroke (IS).
- (c)   Comprehensive neurologic and cardiac imaging, lab analyses, and a questionnaire for cardiovascular risk factors and substance use were performed. Thirteen patients tested positive for THC in urine and had previously described marijuana use.
- (d)   Ten of the 13 users displayed the specific pattern of multifocal intracranial stenosis (MIS).
Ten of eleven with MIS were cannabis users. Of those 5 drank unusually large amounts of alcohol. The association between MIS and marijuana use was highly significant and revealed odds of having used marijuana given MIS is 113 times the odds of not having used marijuana (OR=113, 95% CI: 9-5047, p<0.001).
- (e)   An exact logistic regression model demonstrated no other factor could be introduced into the model and no other factor appeared to be related independently to MIS.

1 low quality finding (Geller et al., 2004)
- (a)   Conducted at the Departments of Neurology, Pediatrics, and Pathology, St. Louis University
School of Medicine, St. Louis, MO, USA
- (b)   A case-series describing the clinical characteristics, radiologic findings, and neuropathological features of THC related posterior fossa ischemic stroke in adolescent patients.
- (c)   Cases included 3 male adolescent cases aged 15, 16, and 17 that all had confirmed acute infarctions and localized to the cerebellum. Two of the three cases died. Two associated with "binge" marijuana use (not defined). Some generalization about possible mechanism of injury: marijuana exposure contributes to cerebellar vascular injury, possibly by vasospasm, especially in the inexperienced or episodic marijuana user, which results in cerebellar ischemia.

Supportive Evidence:
1 low quality finding (Barber et al., 2013)
- (a)   Conducted at the Departments of Neurology, Microbiology, and General Medicine, Auckland
City Hospital, Auckland, New Zealand

(b) Among 218 consecutive patients in a case-control study, ages 18-55, who were admitted to a single New Zealand hospital for ischemic stroke or transient ischemic attack (TIA), 15% of cases tested positive for marijuana in their urine, compared to 8% of control or patients admitted for other reasons excluding stroke.

(c) Risk for stroke or TIA was increased 2.3 (95% CI: 1.08-5.08) fold, but marijuana smokers were also more likely to smoke tobacco, so after adjustment for tobacco use risk was only 59% higher (not statistically significant).

(d) See Appendix A " Proposed Physiologic Effects of Cannabis on the Cardiovascular system

Is marijuana use associated with increased risk of infertility?

SUMMARY STATEMENT 4: We found mixed evidence for whether or not marijuana use increases the risk of male infertility.

Supporting Evidence:
1 low quality finding (Pacey et al., 2014)
(a) The Department of Human Metabolism investigated association of common lifestyle choices with poor sperm morphology.

(b) Recruited from 14 fertility clinics across the UK

(c) Unmatched case-referent study with 318 cases and 1,654 referents. Multilevel logistic regression used to measure associations.

(d) The odds of marijuana use in the 3 months prior to sperm morphology test is 1.55 times as high for those with <4% normal sperm morphology compared to those with >4%sperm morphology. Or in other words, use of cannabis within 3 months prior was associated with 1.55-times higher risk for poor sperm morphology.

(e) Models only adjusted for clustering within clinic, making the OR more of a crude odds ratio. Men seeking fertility therapy may not be representative of men in general.

1 low quality finding (Vescovi et al., 1992).
(a) In an experimental study conducted in Italy, Male adult regular marijuana users have lowered sensitivity to gonadotropins.

(b) There was an association with reduced and Lutenizing Hormone before (5.8 +/- 1.5 vs. 10.5 +/- 1.3 munits/ml; P<0.05) and after injection of GnRH (37.8 +/- 4.4 vs 50.4 +/- 4.9 munits/3hrs; P<0.01).

(c) 10 regular marijuana users who reported using on average 1 g of 1.83% THC per day and 10 nonusers tested for sensitivity to two different mediary hormones involved in spermatogenesis.

(d) Reduced basal levels and secretion of LH in response to GnRH were shown to be significantly reduced among heavy marijuana users.

(e) Experimental studies are not necessarily generalizable but gives biological plausibility for population-based studies.

1 low quality finding (Sun, 2008)
(a) Experimental design mouse model study conducted in Japan.

(b)   Determined the effect of genetic fatty acid amide hydrolase, cannabinoid receptors; brain type and spleen type in fatty acid amide hydrolase- knockout mice (FAAH -/-, CNR1-/-, and CNR2 -/-) in regard to male fertility.

(c)   Wild-type and FAAH -/- female and male mice are bred. A total of 122 litters were observes across the 4 breeding combinations.

(d)   Male FAAH -/- knockout mice, when bred with wild type females have marginally significant reduced litter sizes ($p=0.06$).

(e)   The authors show that genetic loss of FAAH results in elevated levels of anandamide, an endocannabinoid, in the male reproductive system, leading to compromised fertilizing capacity of sperm.

(f)   Retention of FAAH -/-sperm on the egg zona pellucida provides evidence that the capacity of sperm to penetrate the zona barrier is hampered by elevated anandamide levels ($p<0.01$).

(g)   In a male-mouse model, experimental design used to mimic long-term exposure to marijuana resulted in significantly reduced litter size and reduced capacity to penetrate the egg's zona barrier.

Opposing Evidence:

1 low quality finding (Povey et al., 2012)

(a)   The Department of Human Metabolism investigated the association of common lifestyle choices with low sperm count.

(b)   Unmatched case-referent study with 939 cases and 1,310 referents. Cases had a low-motile sperm count ($<12 \times 10^6$ for 3 days of abstinence).

(c)   Men recruited from 14 fertility clinics across the UK

(c)   There was no association between marijuana use and increase or decrease of low-motile sperm count.

(d)   Models are only adjusted for clustering within clinic, making the OR more of a crude odds ratio. Men seeking fertility therapy may not be representative of men in general.

Is marijuana use associated with increased risk of testicular cancer?

SUMMARY STATEMENT 5: We found limited evidence that marijuana use among adult males increases risk of nonseminoma testicular cancer.

Supporting Evidence:

1 medium quality finding (Trabert, 2010)

(a)   In a case-control study heavy use of marijuana was found to be associated with testicular germ cell testicular cancer tumors.

(b)   Conducted at the University of Texas M.D. Anderson Cancer Center

(c)   A greater association was found among men presenting nonseminoma testicular germ cell tumor (TGCT) patients (n = 187) diagnosed between January 1990 and October 1996 and male friend controls (n = 148) were residents of Texas, Louisiana, Arkansas, or Oklahoma and between the ages of 18 and 50 at the time of diagnosis.

(d)   All TGCT patients were more likely than controls to self-report smoking marijuana once or more per day (OR= 2.2, 95% CI: 1.0-5.1). Nonseminoma patients were more likely than controls to self-report smoking marijuana once per or more day (OR=3.1, 95% CI: 1.2-8.2). Nonseminoma patients were more likely than controls to self-report marijuana use 10 years or longer (OR= 2.4, 95% CI: 1.0-6.1).

(e)   Limitations: small cell numbers create low power and wide measures of association, self-reported data, and friend controls could be too similar in regards to lifestyle behaviors.

(f)   Strengths: authors report their prevalence data to be consistent with NSDUH data and these findings are consistent with two other reports.

1 medium quality finding (Daling 2009)

(a)   A case-control study conducted through the Fred Hutchinson Cancer Research Center, Seattle, Washington.

(b)   Cases (n= 371) were men, ages 18 to 44 years, residents of King, Pierce, or Snohomish Counties, Washington state and diagnosed with invasive testicular germ cell tumors (TGCTs). Controls (n = 979) were men without history of TGCT who resided in the same 3 counties as the case diagnosis period and were recruited via random digit dialing and frequency matched to the cases on 5- year age groups using 1-step recruitment.

(b)   Men with TGCT were slightly more likely to have ever smoked marijuana than controls (OR=1.3, 95% CI: 1.0-1.8). Cases were more likely to be current marijuana smokers at the reference date in reference to controls (OR=1.7, 95% CI: 1.1-2.5). Cases who were current users were slightly more likely to have first used under the age of 18 years (OR=1.8, 95% CI: 1.2 -2.8) compared to controls.

(c)   Regarding histological type, associations between current marijuana use compared to never use and TGCT was limited primarily to nonseminomas (OR= 2.3, 95% CI: 1.3-4.0). There appeared to be an increasing risk with length of use greater than or equal to 10 years compared to less than 10 years among current smokers (OR=2.7, 95% CI: 1.5-5.0); and weekly or daily use compared to less than once per week among current marijuana users (OR=3.0, 95% CI: 1.5-5.6).

(d)   Limitations: case-control study, self-reported data, low cell counts give wide measures of association.

(e)   Strengths: good selection of controls, dose-response shown, and results are consistent with two other reports.

1 low quality finding (Lacson, 2012)

(a)   A case-control study conducted through the Department of Preventative Medicine, University of Southern California.

(b)   Testicular germ cell tumor (TGCT) patients (n = 163) who were diagnosed in Los Angeles County from December 1989 to April 1991 were enrolled in the study. Controls (n = 292) were matched on age, race/ethnicity, and neighborhood. Cases were 18 to 35 years at diagnosis (27 +/- 12.7). For each participating case, authors attempted to recruit 4 unaffected male controls for every 1 case matched on date of birth (within 3 years), race, ethnicity, and neighborhood of residence at the time of diagnosis. From 1 to 4 controls were matched for each case.

(c)   Compared with never users, current marijuana users had nonsignificant increase in risk of TGCT (OR=1.38, 95% CI: 0.67-2.87), whereas former users had greater than 2-fold increase in risk (OR=2.28, 95% CI: 1.17-4.43) of TGCT. Ever use of marijuana appeared to be unassociated with risk of seminoma but was associated with greater than 2-fold risk of nonseminoma/mixed GCT (OR=2.42, 95% CI: 1.08-5.42). Associations with nonseminoma/GCT were

more pronounced for former marijuana use (OR= 3.04, 95% CI: 1.29-7.19) than for current marijuana use (OR=2.61, 95% CI: 0.64-4.01). A less than 1/week frequency among former users was associated with over a 3-fold increase in nonseminoma/mixed GCT risk (OR=3.30, 95% CI: 1.34-8.09).

    (d)   Limitations: this study adjusts for religious practices and does not adjust for alcohol or tobacco use.

    (e)   Strengths: one of three similar studies in different locations reporting an association between marijuana use and nonseminoma/mixed GCT and not with seminoma GCT.

Is marijuana use associated with increased risk of bladder cancer?

SUMMARY STATEMENT 6: We found <u>insufficient evidence</u> to determine if marijuana use in adults is associated with transitional cell carcinoma of the bladder.

<u>Supporting Evidence:</u>
1 low-quality finding (Chacko et al., 2006)

    (a)   Case-control study through the Stanford University Medical Center, Department of Urology investigates marijuana use among young (age less than 60 years) transitional cell carcinoma patients with that among age-matched controls.

    (b)   After multivariate adjustment for the other potential risk factors and transitional cell carcinoma, increasing joint-years of marijuana use remained statistically significantly associated with the presence of transitional cell carcinoma ($p < 0.01$). Those who had ever smoked marijuana had a three-fold greater risk of bladder cancer when compared to those who never smoked (OR = 3.4). Those who currently smoke had a nearly two fold greater risk compared to those who never smoked (OR =1.9). Those who had greater than 40 "joint-years" were at 3.5 times greater risk of bladder cancer.

    (c)   "Joint-years" is defined as the product of marijuana joints smoked per day and the number of years the subject smoked marijuana.

    (d)   Reasons for including covariates were based on two studies which employed Vietnam vets as the study population. Models were adjusted only for exposure to Agent Orange, radiation, and dyes.

    (e)   Limitations: Cell numbers are low- only 6 cases and 4 controls reported using only marijuana. Most people who used marijuana also smoked tobacco. Tobacco use was not adjusted for.

Reference finding for those with bladder cancer who smoke tobacco (Freedman, 2011)

    (a)   A large prospective cohort conducted by the NIH.

    (a)   Men (n = 281, 394) and women (n = 186, 134) of the NIH-AARP cohort completed a lifestyle questionnaire and were followed from 1995 through 2006. Respondents lived in one of 8 states: California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania

    (b)   During 4,518,938 years of follow-up, incident bladder cancer occurred in 3,896 men and 627 women.

    (c)   The population attributable risk for ever smoking was 0.50 (95% CI: 0.45-0.54) in men and 0.52 (95% CI: 0.45-0.59) in women

    (d)   About half of all bladder cancers in the cohort population were due to smoking tobacco for both men and women.

Reference finding for bladder cancer rates in the US (Jemal, 2010)
- (a) This report by the American Cancer Society examines cancer incidence, mortality, and survival by site, sex, race/ethnicity, geographic area, and calendar year.
- (a) In 2010, incidence of bladder cancer was 70,530. Of those, 52,760 were men and 17,700 were women.

Opposing Evidence:
1 medium quality finding (Sidney, 1997)
- (a) Examine the relationship of marijuana use to cancer incidence.
- (b) Kaiser Permanente retrospective cohort study, comprised of a population of 64,855 Kaiser Permanente Medical Care Program members, aged 15 to 49 years (mean 33 years) in Oakland and San Francisco who completed an index health visit from 1979 to 1985.
- (c) Retrospective cohort: Cox proportional hazards models were used to examine the joint effect of sociodemographic characteristics, marijuana use, tobacco, and alcohol use on the risk of cancer, from which estimates of relative risks were obtained.
- (d) Ever use of marijuana was not associated in men or women with increased or decreased risk of bladder cancer

Is marijuana use associated with increased risk of prostate cancer?

SUMMARY STATEMENT 7: We found limited evidence marijuana use is associated with increased risk of prostate cancer.

Supporting Evidence:
1 medium quality study (Sidney, 1997)
- (a) Examine the relationship of marijuana use to cancer incidence.
- (b) Same previously mentioned Kaiser Permanente retrospective cohort comprised of a population of 64,855 Kaiser Permanente Medical Care Program members, aged 15 to 49 years (mean 33 years) in Oakland and San Francisco who completed an index health visit from 1979 to 1985.
- (c) Retrospective cohort: Cox proportional hazards models were used to examine the joint effect of sociodemographic characteristics, marijuana use, tobacco, and alcohol use on the risk of cancer, from which estimates of relative risks were obtained.
- (d) Current marijuana use was associated with increased risk of prostate cancer (RR= 4.7, 95% CI: 1.4-15.5). Duration of use was not associated with the risk of any cancer site or grouping of cancers.

OTHER TOPICS RESEARCHED

- Kidney disease
  - One case of a 29-year old man admitted to Royal Liverpool Hospital in London with acute renal infarction who reported 10 years of marijuana use and the day before he had smoked several cigarettes and drunk several bottles of beer (Lambrecht, 1995).
- Liver disease

- o Mixed evidence and overarching issue of temporality of marijuana use and liver disease, does liver disease cause marijuana use or does marijuana use cause liver disease.
  - o Reviewed the following articles and majority of discussions were marijuana use for treatment of symptoms caused by liver disease treatments, mainly Hepatitis C Virus treatment.
    - ▪ (Hézode et al., 2008, Ishida et al., 2008, Russell et al., 2014, Liu et al., 2014, Brunet et al., 2013, Ranney et al., 2009, Nickels et al., 2007, Sylvestre et al., 2006, Hézode et al., 2005, Whitfield et al., 1997)
- Risk of infectious disease
  - o Plausible, suppression of immune system
  - o True effect, risky behavior, or shared exposure
- Other cancers (not testicular, lung, or oral-pharynx)

OTHER ISSUES

- Cannabinoid Hyperemesis
  - o Limited to case-series evidence
  - o Not enough data to make a public health statement
- Cannabinoid Arteritis
  - o Several mentions of "Buerger's- like" disease, however there is currently not enough evidence to make a public health statement

REFERENCES

Ahmed I. A., A., van den Elsen, G. A. H., van der Marck, M. A., & Rikkert, M. G. M. O. (2014). Medicinal use of cannabis and cannabinoids in older adults: where is the evidence? *JAGS*, *62*(2), 410–411.

Barber PA, Pridmore HM, Krishnamurthy V, Roberts S, Spriggs DA, Carter KN, Anderson NE, Cannabis, Ischemic Stroke, and Transient Ischemic Attack, A Case-Control Study. Stroke 2013; 44-2327-2329.

Banerjee A, Singh A, Srivastava P, Turner H, Krishna A. Effects of chronic bhang (cannabis) administration on the reproductive system of male mice. Birth Defects Res B Dev Reprod Toxicol 2011;**92**(3):195-205 doi: 10.1002/bdrb.20295

Brunet, L., Moodie, E. E. M., Rollet, K., Cooper, C., Walmsley, S., Potter, M., & Klein, M. B. (2013). Marijuana smoking does not accelerate progression of liver disease in HIV-hepatitis C coinfection: a longitudinal cohort analysis. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *57*(5), 663–70. doi:10.1093/cid/cit378

Chacko JA, Heiner JG, Siu W, Macy M, Terris MK. Association between marijuana use and transitional cell carcinoma. Urology.2006;67(1):100-104.

Chiolero, A., & Schmid, H. (2002). Repeated self-reported injuries and substance use among young adolescents: the case of Switzerland. *Sozial- Und Präventivmedizin*, *47*(5), 289–97. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12512222

Chipman ML, Macdonald S, Mann RE. Being "at fault" in traffic crashes: Does alcohol, cannabis, cocaine, or polydrug abuse make a difference? Inj Prev 2003;9:343– 8.

Daling JR, Doody DR, Sun X, et al. Association of marijuana use and the incidence of testicular germ cell tumors. Cancer. 2009;115(6):1215–23. doi:10.1002/cncr.24159.

Frost L, Mostofsky E, Rosenbloom JI, Mukamai KJ, Mittleman MA. Marijuana Use and Long-Term Mortality among Survivors of Acute Myocardial Infarction. American Heart Journal. 2013; February; 165(2) 170-175.

Hézode, C., Zafrani, E. S., Roudot-Thoraval, F., Costentin, C., Hessami, A., Bouvier-Alias, M., … Mallat, A. (2008). Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology*, *134*(2), 432–9. doi:10.1053/j.gastro.2007.11.039

Ishida, J. H., Peters, M. G., Jin, C., Louie, K., Tan, V., Bacchetti, P., & Terrault, N. A. (2008). Influence of cannabis use on severity of hepatitis C disease. *Clinical Gastroenterology and Hepatology*, *6*(1), 69–75.

Jouanjus E, Lapeyre-Mestre M, Micallef J, Cannabis Use: Signal of Increasing Risk of Serious Cardiovascular Disorders. Journal of the American Heart Association. 2014;3:e000638

Lacson JCA, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortesis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer. 2012;118(21):5374–83. doi:10.1002/cncr.27554.

Liu, T., Howell, G. T., Turner, L., Corace, K., Garber, G., & Cooper, C. (2014). Marijuana use in hepatitis C infection does not affect liver biopsy histology or treatment outcomes. *Canadian Journal of Gastroenterology & Hepatology*, *28*(7), 381–4. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25157529.

Mittleman MA, Lewis RA, MacClure M, Sherwood JB, Muller JE. Circulation. 2001; 103:2805-2809.

Mukamal KJ, MacClure M, Muller JE, Mittleman MA. An Exploratory Prospective Study of Marijuana Use and Mortality Following Acute Myocardial Infarction. American Heart Journal 2008, March; 155(3) 465-470.

Nickels, M., Jain, A., Sharma, R., Orloff, M., Tsoulfas, G., Kashyap, R., & Bozorgzadeh, A. (2007). Polysubstance abuse in liver transplant patients and its impact on survival outcome. *Experimental and Clinical Transplantation : Official Journal of the Middle East Society for Organ Transplantation*, *5*(2), 680–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18194121

Pacey AA, Povey AC, Clyma JA, et al. Modifiable and non-modifiable risk factors for poor sperm morphology. Hum Reprod 2014;**29**(8):1629-36 doi: 10.1093/humrep/deu116

Ranney, D. N., Acker, W. B., Al-Holou, S. N., Ehrlichman, L., Lee, D. S., Lewin, S. a, … Englesbe, M. J. (2009). Marijuana use in potential liver transplant candidates. *American Journal of Transplantation : Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, *9*(2), 280–5. doi:10.1111/j.1600-6143.2008.02468.x

Russell, M., Pauly, M. P., Moore, C. D., Chia, C., Dorrell, J. M., Cunanan, R. J., & Witt, G. (2014). The impact of lifetime drug use on hepatitis C treatment outcomes in insured members of an integrated health care plan. *Drug and Alcohol Dependence*, *134*, 222–7. doi:10.1016/j.drugalcdep.2013.10.001

Sidney S, Jr. CPQ, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). Cancer Causes Control. 1997;8(5):722–728. doi:10.1023/A:1018427320658.

Sun X, Wang H, Okabe M, et al. Genetic loss of Faah compromises male fertility in mice. Biol Reprod 2009;**80**(2):235-42 doi: 10.1095/biolreprod.108.072736

Sylvestre, D. L., Clements, B. J., & Malibu, Y. (2006). Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. *European Journal of Gastroenterology & Hepatology*, *18*(10), 1057–63. doi:10.1097/01.meg.0000216934.22114.51

Terhune KW, Ippolito CA, Hendricks DL, Michalovic JG, Bogema SC, Santinga P, et al. The incidence and role of drugs in fatally injured drivers. DOT HS-808-065. US Department of Transportation, National Highway Traffic Safety Administration, 1992.

Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA. Marijuana use and testicular germ cell tumors. Cancer. 2011;117(4):848–53. doi:10.1002/cncr.25499.

Vescovi PP, Pedrazzoni M, Michelini M, Maninetti L, Bernardelli F, Passeri M. Chronic effects of marihuana smoking on luteinizing hormone, follicle-stimulating hormone and prolactin levels in human males. Drug Alcohol Depend 1992;**30**(1):59-63

Wolff V, et. al. Cannabis Use, Ischemic Stroke, and Multifocal Intracranial Vasoconstriction: A Prospective Study of 48 Consecutive Young Patients. Stroke, 2011; 42,1778-1780.

Zautcke, J. L., Coker, S. B., Morris, R. W., & Stein-Spencer, L. (2002). Geriatric trauma in the State of Illinois: Substance use and injury patterns. *The American Journal of Emergency Medicine*, *20*(1), 14–17. doi:10.1053/ajem.2002.30107

Appendix A "Proposed Biological Effects of Marijuana

1) **Mittleman, MA: Triggering Myocardial Infarction by Marijuana, Circulation, 2001;103:2805-2809.   US   page 2808.**
- Smoking marijuana is associated with a dose-dependent increase in heart rate. (2–10)
- Typical increases in heart rate associated with a single marijuana cigarette range from 20% to 100%, with the peak in heart rate occurring 10 to 30 minutes after beginning to smoke.(2,4,6–8)
- Most subjects experience an increase in blood pressure, particularly when supine.(3,6,7,9)
- Postural hypotension after smoking marijuana is not uncommon.(5,9,27)
- Tolerance to the hemodynamic effects of marijuana can occur with frequent repeated use.(27,28) In addition to the hemodynamic effects, smoked marijuana is associated with an increase in carboxyhemoglobin, resulting in decreased oxygen-carrying capacity.(3,5,11)
- Marijuana may increase factor VII activity (29)
- Smoking marijuana is associated with an increase in myocardial oxygen demand and a concomitant decrease in oxygen supply.

2) **Mukamal KJ, An Exploratory Prospective Study of Marijuana Use and Mortality Following Acute Myocardial Infarction. American Heart Journal, 2008 March; 155(3); 465-470   US   page 5**
- Increase in resting heart rate that can be selectively blocked by pretreatment with a cannabinoid receptor antagonist. (26)
- May be related to the prolonged catecholamine release that marijuana can induce.(27)
- Marijuana use can also increase supine blood pressure, although it leads to orthostatic hypotension, postural dizziness, and even syncope in some cases.(28, 29)
- Marijuana increases heart rate and, therefore, myocardial oxygen demand, it may also limit oxygen uptake.
- Marijuana smoking leads to a dose-dependent increase In carbon monoxide exposure (30) and higher blood levels of carboxyhemoglobin than cigarette smoking.(12)
- These effects have a demonstrably detrimental impact on patients with known coronary heart disease, in whom marijuana use decreases exercise time to the onset of angina by 50%, twice as great an effect as use of a standard cigarette.(31)

3) **Frost L, Marijuana use and long-term mortality among survivors of acute myocardial infarction. American Heart Journal, (2013)165:170-5   US**
- Marijuana acutely increases blood pressure, probably mediated through sympathetic stimulation and reduced parasympathetic activity.(29)

- This rise in norepinephrine increases myocardial oxygen demand and reduced left ventricular ejection time, thereby lowering the threshold for angina and peripheral vascular resistance in skeletal muscles.(30)
- In addition, the increase carbon monoxide exposure from marijuana smoking results in even higher blood levels of carboxyhemoglobin than does smoking standard cigarettes.(31)

4) **Jouanjous, E. Cannabis Use:Signal of Increasing Risk of Serious Cardiovascular Disorders Journal of the American Heart Association; 2014;3:e000638 FRANCE page 6**
- Long-term use of cannabis should be responsible for long-lasting decreased blood pressure, heart rate and cardiac contractility; increased blood volume; and diminished circulatory responses to exercise It is associated with decreased myocardial function. These are consistent with centrally-mediated, reduced sympathetic and enhanced parasympathetic activity.(43)
- The opposite can be observed in pathologic cardiovascular conditions: in animals, THC was shown to be responsible for vasoconstriction. Now, vasospasm could be a possible common origin for many of the cases we describe in the present study.
- The direct impact of cannabinoids on factors such as nitric oxide or endothelial factors could explain the disparity of complications observed between cannabis and tobacco.(44)

5) **Gaziano, JM, Marijuana use among those at risk for cardiovascular events. American Heart Journal, 2008 155:395-396. US**
- MJ use increases carboxyhemoglobin levels, decreasing oxygen-carrying capacity and with it exercise capacity. The increases in carboxyhemoglobin levels are larger than those seen with smoking a cigarette.
- Smoking marijuana immediately increases catecholamines.
- It increases the heart rate quickly, and the effect lasts for 2 to 3 hours.
- Marijuana has also been associated with immediate increases in blood pressure, and in some cases, the increase is dramatic.
- Cardiac function is also altered for a period of hours after smoking. Left ventricular ejection time decreases, filling time decreases (along with an increased sinus rate), and atrial nodal conduction is facilitated.(5)
- In some cases, systemic vascular resistance decreases and may explain the profound postural hypotension seen in some.
- In addition, long-term use may decrease high-density lipoprotein cholesterol and lead to increased energy intake.(7)

6) **Aryana, A, Marijuana as a trigger of cardiovascular events: Speculation or scientific certainty ? International Journal of Cardiology, 118 (2007) 141-144   US**
   - Whether delivered intravenously or through smoking, THC can result in a rapid and substantial dose-dependent increase in heart rate by as much as 20–100% and a modest increase in blood pressure [3–10].
   - These effects are believed to be mediated through sympathetic stimulation and reduced parasympathetic activity, with the maximal increase generally seen within 15 min after a peak THC plasma concentration   and lasting for up to 3 h [3,5].
   - THC can increase cardiac output by as much as 30% or more [3,8].
   - THC facilitates atrioventricular node conduction, reduce left ventricular ejection time, and decrease peripheral vascular resistance particularly in the skeletal muscle [3,8].
   - Orthostatic hypotension has been frequently associated with marijuana use and both syncope and near-syncope can occur [3,4,11,12].

Table 1

Marijuana, THC, and cardiovascular events: proposed mechanisms

• Proarrhythmic effect mediated by catecholamines

• Cardiac ischemia due to an increase in heart rate and cardiac workload in susceptible individuals

• Postural hypotension

• Delay in seeking medical care for acute coronary events due to analgesic properties of THC

• Impaired oxygen supply to the heart secondary to increased blood carboxyhemoglobin levels

• Production of oxidant gases by marijuana smoking resulting in cellular stress, which may heighten cardiovascular risk through activation of platelets, increased oxidized LDL formation, enhanced factor VII activity, and induction of an inflammatory response

7) **Bachs L, Acute cardiovascular fatalities following cannabis use. Forensic Science International 124 (2001) 200-203. NORWAY   page 201-2**
   - Cardiovascular effects are the most consistent physiological findings after acute cannabis administration.
   - Significant tachycardia
   - Increased limb blood flow with postural hypotension have been reported.

- Effects are likely to be mediated via b – adrenergical stimulation and possibly also a parasympathetic nervous system blockade [12–15].
- A catecholamine increase will lead to an increased oxygen demand in the myocardium, constituting a potential threat to patients with an ischaemic heart condition [1,12,16]."

References:

Aryana, A. and M. A. Williams (2007). "Marijuana as a trigger of cardiovascular events: speculation or scientific certainty?" Int J Cardiol **118**(2): 141-144.

Bachs, L. and H. Mørland (2001). "Acute cardiovascular fatalities following cannabis use." Forensic Science International **124**(2-3): 200-203.

Frost, L., E. Mostofsky, J. I. Rosenbloom, K. J. Mukamal and M. a. Mittleman (2013). "Marijuana use and long-term mortality among survivors of acute myocardial infarction." American heart journal **165**(2): 170-175.

Gaziano, J. M. (2008). "Marijuana use among those at risk for cardiovascular events." Am Heart J **155**(3): 395-396.

Jouanjus, E., M. Lapeyre-Mestre, J. Micallef, A. French Association of the Regional and C. Dependence Monitoring Centres Working Group on Cannabis (2014). "Cannabis use: signal of increasing risk of serious cardiovascular disorders." J Am Heart Assoc **3**(2): e000638.

Mittleman, M. a., R. a. Lewis, M. Maclure, J. B. Sherwood and J. E. Muller (2001). "Triggering Myocardial Infarction by Marijuana." Circulation **103**(23): 2805-2809.

Mukamal, K. J., M. Maclure, J. E. Muller and M. a. Mittleman (2008). "An exploratory prospective study of marijuana use and mortality following acute myocardial infarction." American heart journal **155**(3): 465-470.

Marijuana Use and Injury

Evidence Summary

CDPHE | COLORADO
Department of Public
Health & Environment

Marijuana Use and Injury: Research Questions and Findings

For Consideration by the Colorado Department of Public Health and the Environment Retail Marijuana Public Health Advisory Committee

Ashley Brooks-Russell, PhD, MPH, Katelyn Hall, MPH, Lisa Barker, Madeline Morris

October 20th, 2014

<u>DEFINITIONS AND GENERAL REMARKS:</u>

USE DEFINITIONS:
   Heavy – daily or near daily use
   Regular – weekly or more often
   Occasional – less than weekly

The definition of injury is physical damage to the body resulting from acute exposure to thermal, mechanical, electrical, or chemical energy

Recreational Injuries: Any injury outside of the workplace and not classified as a motor vehicle accident (MVA).

MVA evidence reviewed was limited to epidemiological/observational studies. This consists of case-control studies and the variant known as culpability studies (also known as responsibility analysis or quasi-induced exposure). The evidence prioritizes studies that measured active THC via blood or self-reported acute use.

Experimental studies will not be reviewed in this section because they were reviewed in the dose and drug response meeting in September. Animal studies are not applicable.

As context for assessing risk from marijuana impairment it is instructive to briefly review the crash risk associated with alcohol use (Zador et al. 2000).

1. There is overwhelming evidence for an increased crash risk related to alcohol use. The relationship is dose-dependent such that there is a clear and dramatic increase in risk related to an increase blood alcohol level (BAC). This relationship also varies by age with younger drivers at an elevated risk compared to adult drivers, independent of BAC level (see Figures 1 and 2; Zador et al., 2000).

2. At .08-.10% BAC, the relative risk of a fatal single-vehicle crash is about 11 times greater. Risk of fatal crash increases at BAC levels as low as .02. Relative risk ranges from 2.6-4.6 at a BAC of .065% to 5.8-17.3 at a BAC of .09% (see Figures 1 and 2; Zador et al., 2000).

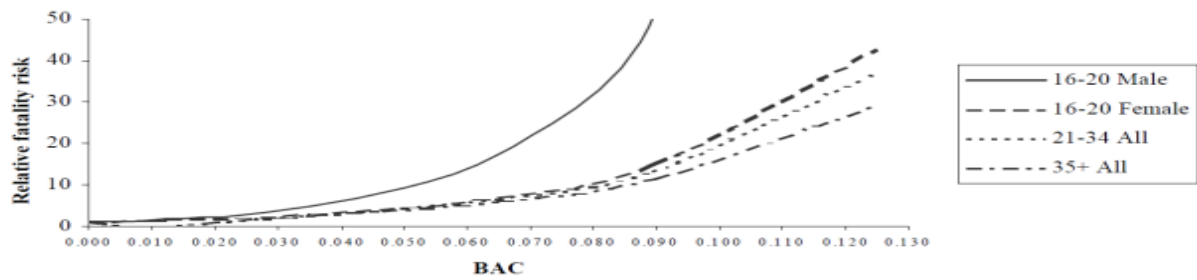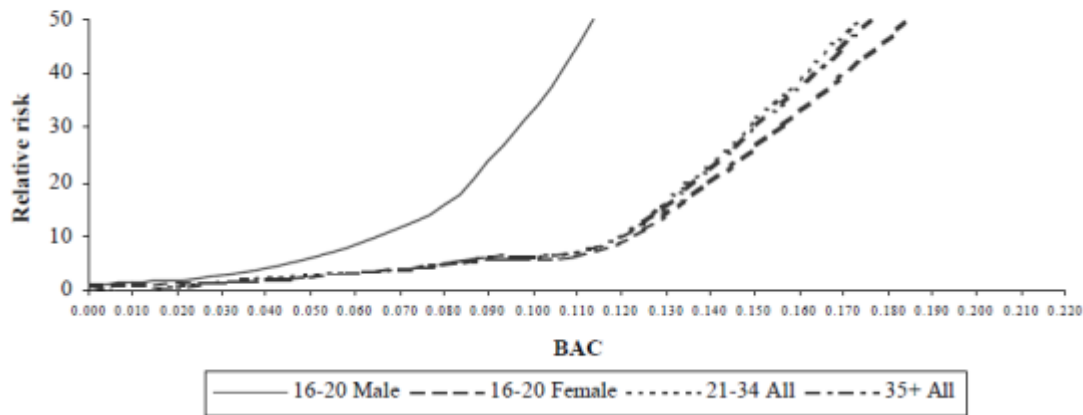Figure 1. Relative fatality risk for drinking drivers by age and sex in single-vehicle crashes[6]

Figure 2. Relative risk for the involvement of drinking drivers by age and sex in all passenger vehicle crashes[7]

Reference: Zador PL, Krawchuk SA, Voas RB. (2000). Relative risk of fatal and crash involvement by BAC, age and gender. US Department of Transportation, National Highway Traffic Safety Administration. DOT HS 809 050.

EPIDEMIOLOGY OF IMPAIRED DRIVING

1. After alcohol, marijuana is the most commonly detected drug among drivers.
2. 2012 National Survey on Drug Use and Health (SAMHSA)
    A. 4% of adult respondents (12% of 18-25 year olds) reported driving under the influence of illicit drugs in the past year. This is compared to 11% of adults (18% of 18-25 year olds) reporting driving under the influence of alcohol.
3. 2007 National Roadside Survey (NHTSA)
    A. 16.3% of weekend, nighttime drivers tested positive for illegal, prescription, or over-the-counter drugs.
    B. 8.6% of nighttime weekend drivers tested positive for marijuana (level not available) compared to 2.2% had BAC > .08 g/dL.
4. Colorado Department of Transportation. (2013). Drugged Driving Statistics
    http://www.coloradodot.info/programs/alcohol-and-impaired-driving/druggeddriving/drugged-driving-statistics.html
        1. In 2012, 12.2% of those drivers tested for drugs were positive for THC only.

<u>RESEARCH QUESTIONS AND FINDINGS</u>

How does marijuana use increase the risk of a car crash?

SUMMARY STATEMENT 1): We found <u>substantial evidence</u> that risk of motor vehicle crash doubles among drivers with recent marijuana use.

    <u>Supporting Evidence:</u>
    1 high quality finding from a meta-analysis (Asbridge et al., 2012)
        (a)   9 studies that assessed acute or recent marijuana use by the toxicological analysis of whole blood or via self-report (use within 3 hours before crash)
        (b)   Case control studies included hospital studies, roadside studies, studies of collisions (including fatal collision) drawn from police records, and self-report studies
        (c)   Assessed quality using Newcastle-Ottawa scale
        (d)   Pooled risk of marijuana: OR = 1.92 (95% CI: 1.35-2.73)

    1 high quality finding from a systematic review (Hartman & Huestis, 2013)
        (a)   Reviewed epidemiological literature as well as experimental literature (also referenced in the prior dose and drug response presentation). Identified 10 epidemiologic studies from 6 counties with reported effects ranging from OR's of 1.29 to 6.6. Authors suggest a "doubling" of crash risk

    <u>Opposing Evidence</u>:
    1 low quality study (Lowenstien & Koziol-McLain, 2001)
        (a) Used urine samples (not blood) to ascertain presence of legal and illegal drugs among 414 injured drivers who presented to an ED department within 1 hour of a crash. Sub-analysis on 10 subjects did not find a significant relationship between active THC and crash responsibility (OR: 0.7 , 95% CI: 0.1-3.3).

SUMMARY STATEMENT 2): We found <u>substantial evidence</u> for a positive relationship between THC blood level and motor vehicle crash risk.

    <u>Supporting Evidence:</u>
    2 high quality findings
        (a)   Laumon et al. (2005) found an increased OR from 2.18 for THC level of < 1 ng/ml to an OR of 4.72 for THC > 5 ng/ml (with gradation in between).
        (b)   Drummer et al. (2004) found an increased OR from 2.7 for any level of THC to an OR of 6.6 for THC > 5 ng/ml.

How does marijuana use increase the risk of a car crash for occasional users? Heavy users?

SUMMARY STATEMENT 3: We found <u>insufficient evidence</u> to suggest that motor vehicle crash risk differs for occasional users as compared to heavy users.

Notes on Evidence:

(1) Experimental studies (reviewed in the dose and drug response presentation) suggest that occasional users experience greater driving impairment than heavy/chronic users from equivalent doses.

(2) Epidemiological studies rarely assess patterns of use (e.g., fatality studies make this an impossibility).

(3) More frequent self-report used (e.g., substance dependence treatment patients) has been associated with more frequent crash risk, although the measurement of the effects were not acute. (Chipman et al., 2003; Mann et al., 2007; Pulido, et al., 2011).

(4) 1 medium quality study found an association between habitual marijuana use (plus acute use) and crash injury after adjusting for confounders (Blows et al., 2005).

How does combined use of marijuana and alcohol increase risk of motor vehicle accidents?

SUMMARY STATEMENT 4: We found substantial evidence that the combined use of marijuana and alcohol increases motor vehicle crash risk more than either substance alone.

Supporting Evidence:
2 high quality findings

(a) Laumon et al. (2005) estimate the adjusted joint effect corresponding to blood concentrations of both THC and alcohol present at any dose to be 14.0 (8.00 to 24.7) This is very close to the value obtained from the product of the adjusted individual effects (1.78 x 8.51 =15.1), but not a statistically significant interaction.

(b) Drummer et al. (2004) found a significantly stronger positive association with drivers positive to THC and with BAC ≥0.05% compared with BAC ≥0.05 alone (OR 2.9, 95% CI: 1.1–7.7).

1 medium quality finding

(a) Mura et al. (2003) analyzed a case-control study to compare the prevalence of THC among 900 injured drivers and 900 control subjects that were recruited from emergency departments in six French hospitals. THC alone = (OR) of 2.5. In cases where both THC and alcohol (BAC > 0.05%) were present, the OR increased to 4.6.

Is there a higher incidence of non-traffic related injuries among adults who use marijuana?

SUMMARY STATEMENT 5: We found mixed evidence for whether or not adults who use marijuana are at a higher risk of non-traffic related injuries.

WE HAD HOPED TO STRATIFY ADULTS INTO THREE CATEGORIES: YOUNG ADULT (up to 25 years), ADULT (26-64 years), AND OLDER ADULTS (>65 years). WE WERE UNABLE TO DISSECT THE LITERATURE IN THIS WAY.

Supporting Evidence:
1 medium quality finding (Gerberich et al., 2003)

(a) Conducted by the Division of Environmental and Occupational Health, Regional Injury Prevention Research Center and Center for Violence Prevention and Control, School of Public Health, University of Minnesota, Minneapolis, MN.
(b) In a retrospective cohort, Gerberich et al. examined baseline self-reported marijuana use and ten-year incidence of hospitalized injury, categorized into all injury, falls, motor vehicle, struck against, assaults, and self-inflicted.
(c) Study population were Kaiser Permanente members aged 15 to 49 that completed a multiphasic health checkup (MHC) with self-reported questionnaire on marijuana use (never, former, current) and demographics in Northern California between1979 to1985 (N=965).
(d) Mean follow-up was 6.72 +/- 3.87 years.
(e) Used Poisson regression to calculate adjusted incidence rate ratios (adjusted for age, race, education, marital status, BMI, diagnosed medical condition, smoking status, and alcohol use).
(f) Adjusted analyses showed increased ten-year incidence rate-ratios for all-cause injury hospitalizations in both men (RR=1.28, 95% CI: 1.01-1.61) and women (RR=1.37, 95% CI: 1.04-1.79) among current marijuana users compared to nonusers. Cause-specific incident rate-ratios were increased for assault (RR=1.90, 95% CI: 1.16-3.15) among men in current marijuana users compared to never users.

1 low quality finding (Barrio et al. 2012)
(a) Conducted by Escuela Nacional de Sanidad, Instituto de Salud Carlos III, Monforte de Lemos, 5, 28029 Madrid, Spain.
(b) Cross-sectional data (N=28,324) used in logistic regression to obtain ORs between patterns of marijuana use and frequency of non-traffic related injuries.
(c) An increased reporting of non-traffic related injuries (NTIs) was observed for marijuana users in the past 12 months (OR = 1.4, 95% CI: 1.2-1.7). The magnitude of this association did not change depending on the frequency of consumption. It was higher in the older adult population (OR = 1.8, 95% CI: 1.3-2.4) than in younger people (OR = 1.3, 95% CI: 1.1-1.5), although this difference was not statistically significant. Analysis of type of NTI revealed a strong association between marijuana use and NTIs due to knocks and bumps (OR= 2.0, 95% CI: 1.5-2.5), especially in weekly marijuana users (OR= 5.1, 95% CI: 2.9-8.9). The association with falls was weaker (OR = 1.2, 95% CI: 1.0-1.6). With regards to the place where the injury occurred, an increase of NTI reports occurring at work was observed in marijuana users. However, the association with NTI occurring outside work was more clear (OR = 1.4, 95% CI: 1.2-1.7), being especially high among weekly marijuana users in adults aged 35-64 (OR = 3.0, 95% CI: 1.8-4.9).
(d) Self-reported drug use may have led to an underestimation of marijuana consumption. Subjects only explored their injury history requiring medical assistance, excluding all minor injuries and some major injuries not attended in health care facilities.
(e) Risk attitude was not adjusted for and has been in previous studies.
(f) Men and women were evenly selected for within each age group. This had the potential to diminish an association towards the null because it is well known that men tend to use more than women.

1 low quality finding (Wadsworth et al., 2006)

    (a)   Conducted by the Centre for Occupational and Health Psychology, Cardiff University, UK.

    (b)   Conducted a cross-sectional study examining association between marijuana use and accidents, injuries, and cognitive failures in a workplace and non-work place setting.

    (c)   Data was collected through a self-report questionnaire. Those who reported using other illicit drugs with marijuana were excluded from the analysis.

    (d)   Other risks include: age, sex, income, education, personality (neuroticism, risk taking), mental health (anxiety, depression, sleep problems), physical health (14 day symptoms, 12 month symptoms, chronic symptoms, general health), lifestyle (smoking, alcohol), work status, combined incidents, risk taking at work, work stress, total negative score, social class, employment, experience.

    (e)   Levels of these risk factors were categorized into high and low levels.

    (f)   High levels of other risks and marijuana use was significantly associated with any non-work incident (accidents, road traffic accidents, minor injuries, or cognitive failures) (OR= 4.28, 95% CI: 3.36-5.46, p<0.0001) in 4,895 of the 7,979 that completed the study. This finding was supported by individual analysis of high levels of other risks and marijuana use and minor injuries outside workplace (OR=7.84, 95% CI: 5.55-11.07, p<0.0001) and accidents outside workplace (OR=3.16, 95% CI: 2.22-4.49, p=0.02).

1 low quality finding (Polen et al., 1993)

    (a)   Conducted by the Kaiser Permanente Center for Health Research, Portland, Oregon.

    (b)   Compared self-reported marijuana smoking without ever smoking tobacco and risk of an outpatient visit for the three following conditions respiratory, injury, and other in a retrospective cohort (N=902).

    (c)   Subjects completed questionnaires at index health checkup and their medical records were abstracted for outpatient visits in the two years following the index health checkup.

    (d)   Marijuana smokers who did not smoke tobacco had a significant increased risk of outpatient visits for all three conditions: respiratory (RR=1.19, 95% CI: 1.01-1.41), injury (RR=1.32, 95% CI: 1.10-1.57), and other (RR=1.09, 95% CI: 1.02-1.16). Furthermore, those who smoked marijuana for 10-14 years had increased risk of an outpatient visit due to injury (RR=1.35, 95% CI 1.07-1.68). Did not specify the type of injury (Polen et al. 1993).

Opposing Evidence:

1 medium quality finding (Gmel et al., 2009)

    (a)   Conducted by the Alcohol Treatment Center, Laussanne University Hospital, Laussanne, Switzerland.

    (b)   Study population is emergency department patients reporting injury. The 6 hours before injury was the case period and it was compared to the same 6 hours the week prior for the control period.

    (c)   Case-crossover design allowed for measure of risk association and the ability to compare to a reference group.

    (d)   Large sample size (n = 486; 332 men, 154 women)

(e) Risk of injury was associated with marijuana use for those that used marijuana in the six hours prior to injury when compared the control period, the same six hours the prior week (RR = 0.33, 95% CI: 0.12-0.92).

(f) A major limitation in this study is self-reported marijuana use and it is possible that persons who use marijuana were more likely to report use in the control period rather than in the case period. This would bias the results toward a protective or no effect.

1 medium quality finding (Tait et al., 2010)

(b) Conducted by the Centre for Mental Health Research, Austrialian National University, Canberra, Australia.

(c) Prospective study to assess incidence of first-time self-reported brain injuries among 3 cohorts and to examine the relationship between alcohol and marijuana problems at baseline and subsequent brain injury.

(d) There were 3 cohorts. The first had 2,139 participants aged 20-24, the second had 2,354 aged 40-44, and the third had 2,222 aged 60-64. They were followed for four years.

(e) Participants completed a community survey where problematic marijuana use was assessed by answering "yes" to "In the last year have you ever used marijuana/hash more than you meant to," or "Have you felt you wanted or needed to cut down on your marijuana/hash use in the last year?"

(f) Logistic regression was used to estimate relative risks.

(g) Problematic marijuana use at baseline was not associated with brain injury in the four years following baseline.

1 medium quality finding (Braun et al., 1998)

(a) Conducted by St. Mary's/Duluth Clinic Health System, Division of Education and Research, Duluth, MN.

(b) Used a retrospective cohort design to evaluate the relationship between self-reported marijuana use and 3-year incidence of injury among Kaiser Permanente members 15 to 49 years of age in California between 1979 and 1986 (N=4,464).

(c) Participants completed a questionnaire at index visits and their charts were abstracted for injuries in the three years following the index visit.

(d) There were 2,524 outpatient injury events, 22 injury related hospitalizations, 3 injury-related fatalities. 1,611 participants had at least 1 injury related outpatient event: 1,057 had 1, 338 had 2, and 216 had 3 or more injury related outpatient event.

(e) No consistent differences were seen in adjusted analysis between marijuana users and non-users and medically attended injuries within 3 years following index health visit.

Is there a higher incidence of recreational injuries among adult marijuana users?

Recreational Injuries: Any injury outside of the workplace and not classified as a motor vehicle accident.

SUMMARY STATEMENT 6: We found mixed evidence for whether or not adults who use marijuana are at a higher risk of injury due to recreational activity.

Supporting Evidence:

1 medium quality finding (Asbridge et al., 2014)

(a) Conducted by the Department of Community Health and Epidemiology, Dalhousie University, Centre for Clinical Research, Halifax, Nova Scotia, Canada

(b) Examined whether alcohol and marijuana consumption increased crash risk among non-fatally injured bicyclists 18 years or older (N=393) treated in emergency departments from 2009 to 2011.

(c) The case-crossover design use a six-hour period before the bicycle crash as the case period where participants self-reported alcohol and/or marijuana use. This was validated in 153 (39%) of the participants who agreed to give a blood sample for toxicity screening.

(d) Two control periods were established to later validate the models. The first control period alcohol and marijuana consumption was collected via self-report in the six hours before the last time the participant rode his or her bike around the same time of day. The second control condition was the self-reported usual frequency of cycling under the influence of alcohol or marijuana over the previous six months.

(e) Models examined all types of reported marijuana use alone, those with positive THC toxicity screens, self-report marijuana use only, and all marijuana use with any other substance use (including alcohol).

(f) All types of reported marijuana use alone were associated bicycle collision (N=328, OR=2.38, 95% CI: 1.04-5.43). When restricting analysis to only those who provided a blood sample and marijuana use was measured through a positive THC screen, marijuana was associated with bicycle crashes (N=123, OR=9.0 95% CI: 2.09-38.8). When the sample included those that used marijuana alone or with other substances, marijuana was associated with bicycle crashes (N=393, OR=4.11, 95% CI: 1.98-8.51). When marijuana use was measured via self-report only marijuana use was not associated with crash risk (N=328).

(g) When the models were run using the second control condition there were no associations found between marijuana use and bicycle crash.

(h) A major limitation is that exposure of marijuana was measured with self-report data and blood toxicity sample in the case period and through only self-report in the control period. However, if under-reporting is assumed this would bias towards the null making the findings conservative.

Opposing Evidence:

1 low quality finding (Siwani et al., 2014)

(a) Conducted by the Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN, United States.

(b) Examined the epidemiology of mandibular fractures in a cross-sectional study of subgroups of a pediatric population 18 years or younger (N=122).

(c) Compared substance use (tobacco, alcohol, and marijuana) with type of accident that caused mandibular fracture grouped into motor vehicle accidents and assaults, sports-related injuries, and other (included falls, bicycle accidents, power sports-related, or unknown).

(d) There was no statistical difference in the odds of having a history of substance use when comparing the 3 categories of mechanism of mandibular fracture. Small cell sizes in substance use was a limitation

1 low quality finding (Chiolero et al., 2014)
    (a)   Conducted by the Swiss Institute for the Prevention of Alcohol and Drug Problems (SIPA), Lausanne, Switzerland.
    (b)   Examined the hypothesis that an association exists between the use of substances and repeated injuries in a cross-sectional WHO national study.
    (c)   Population included children in Switzerland aged 12 to 15 (N=7,196) that completed the self-completed questionnaire.
    (d)   Only those aged 14 to 15 completed the marijuana question and use of marijuana included taken a joint, pot, grass, cone, marijuana, or hashish once or more.
    (e)   Logistic regression was used to estimate ORs adjusting for age and socio-economic status.
    (f)   Crude ORs showed that use of marijuana at least once was not associated with three or more injuries in prior 12 months in males, but was associated with three or more injuries in prior 12 months in females (OR=1.80, 95% CI: 1.13-2.86, p<0.05) compared to never users; however, no associations between use of marijuana at least once and three or more injuries in the prior 12 months was observed in the adjusted models.

Does combined substance (marijuana and alcohol) use increase risk of injury among adults?

SUMMARY STATEMENT 7: We found <u>mixed evidence</u> for whether or not adults who use marijuana and alcohol are at a higher risk of injury than use of either substance alone.

<u>Supporting Evidence</u>:
1 medium quality finding (Asbridge et al., 2014)
    (a)   Conducted by the Department of Community Health and Epidemiology, Dalhousie University, Centre for Clinical Research, 4th Floor, 5790 University Avenue, Halifax,   Nova Scotia, B3H 1V7, Canada
    (b)   Examined whether marijuana consumption combined with other substances increased crash risk among non-fatally injured bicyclists 18 years or older (N=393) treated in Canadian emergency departments from 2009 to 2011.
    (c)   Among those that used marijuana alone or with other substances, marijuana was associated with bicycle crashes (N=393, OR=4.11, 95% CI: 1.98-8.51).

1 low quality finding (Woolard et al., 2003)
    (a)   Conducted by Brown University Medical School, Rhode Island Hospital, Injury and Prevention Center, Center for Alcohol and Addiction Studies, and School of Social Studies, Providence, RI, United States.
    (b)   Cross-sectional study among emergency department patients (N = 433) that were problem drinkers with either measurable BAC, report of drinking, or alcohol use disorder.
    (c)   Participants were asked to recall if they had one of 18 injuries in the previous 12 months.
    (d)   Among problem drinkers, the risk of an alcohol-related injury in the past year was higher when marijuana was used at some point in the previous 3 months when compared not reporting a previous injury (OR = 2.26; 95% CI: 1.25-3.75).

Marijuana use was not found to be a predictor of type of injury when adjusted for.

(e)   Marijuana use was not collected for temporal association to the injury.
(f)   A strength is its large sample size and good collection of data.

Opposing Evidence:
1 medium quality finding (Gmel et al.. 2009)
(a)   Conducted by the Alcohol Treatment Center, Laussanne University Hospital, Laussanne, Switzerland.
(b)   Study population is ED patients reporting injury. The 6 hours prior to injury was compared to the same 6 hours the week prior as the case and control periods, respectively.
(c)   There was no association found between the risk of injury and the joint use of marijuana and alcohol (RR = 0.71, 95% CI: 0.12-4.26)

1 medium quality finding (Gerberich et al., 2003)
(a)   Conducted by the Division of Environmental and Occupational Health, Regional Injury Prevention Research Center and Center for Violence Prevention and Control, School of Public Health, University of Minnesota, Minneapolis, MN.
(b)   In a retrospective cohort, Gerberich et al examined baseline self-reported marijuana use and ten-year incidence of hospitalized injury, categorized into all injury, falls, motor vehicle, struck against, assaults, and self-inflicted.
(c)   Study population were Kaiser Permanente members aged 15 to 49 that completed a multiphasic health checkup (MHC) with self-reported questionnaire on marijuana use (never, former, current) and demographics between 1979 to 1985 (N=965).
(d)   Mean follow-up 6.72 +/- 3.87 years.
(e)   Use Poisson regression to calculate adjusted incidence rate ratios (adjusted for age, race, education, marital status, BMI, diagnosed medical condition, smoking status, and alcohol use).
(f)   No potential interactions were found between marijuana use and alcohol use.

Do marijuana users experience a higher incidence of workplace injuries (non-driving)?

SUMMARY STATEMENT 8: We found limited evidence that marijuana use increases workplace injury risk (non-driving injury).

Supporting Evidence:
1 low quality finding (Wadsworth et al., 2006)
(a)   Conducted by the Centre for Occupational and Health Psychology, Cardiff University, 63 Park Place, Cardiff, Cf10 3AS, UK.
(b)   Conducted a cross-sectional study examining association between marijuana use and accidents, injuries, and cognitive failures in and outside the workplace.
(c)   Data was collected through a self-report questionnaire. Those who reported using other illicit drugs with marijuana were excluded from the analysis.
(d)   Other risks include: age, sex, income, education, personality (neuroticism, risk taking), mental health (anxiety, depression, sleep problems), physical health (14 day symptoms, 12 month symptoms, chronic symptoms, general health), lifestyle (smoking, alcohol), work status, combined incidents, risk taking at work, work stress, total negative score, social class, employment, experience.
(e)   Levels of these risk factors were categorized into high and low levels.

(f)   High levels of other risks and marijuana use was marginally significantly associated with any work incident (accidents, road traffic accidents, minor injuries, or cognitive failures) (OR= 4.89 95% CI: 3.42-6.99, *p*=0.04) in 2,859 of the 7,979 that completed the study. This finding was supported by individual analysis of high levels of other risks and marijuana use and minor injuries at work (N=2,801, OR=8.49, 95% CI: 5.37-13.42, *p*=0.001) and accidents at work (N=2,801, OR=3.85, 95% CI: 1.89-7.82, *p* value not given)

1 low quality finding (Shipp et al., 2005)
(a)   Conducted by the Center for Health Promotion and Prevention Research, University of TexasHealth Science Center, Houston, TX, USA. Cross-sectional study examining the association between self-reported non-fatal occupational injuries among high school students and their self-reported general use of substances.
(b)   Population was 23 south Texas high schools in 14 counties (N= 3,265). Those that ever worked N=1501 and ever injured at work N=655.
(c)   In multiple logistic regression analysis, the risk of occupational injury and having used marijuana 1-9 times, 10-29 times, and 40+ times during the past thirty days was increased compared to no use with ORs of 1.37 (95%CI: 1.06-1.77) , 1.51 (95% CI: 1.03-2.21), and 2.47 (95% CI: 1.64-3.71), respectively.

Opposing Evidence:
1 low quality finding (Price et al., 2014)
(a)   Conducted at St. Mary's Occupational Medicine Clinic, Evansville, IN, USA
(b)   Case-control study comparing the proportion of positive urine specimens for THC post-accident versus random samples.
(c)   Of the 3,795 total samples, 351 had positive urine samples for THC and 77 occurred in post-accident screens.
(d)   There was a non-significant association (OR=0.81, 95% CI: 0.62-1.06).

REFERENCES

Asbridge, M., Mann, R., Cusimano, M. D., Tallon, J. M., Pauley, C., & Rehm, J. (2014). Cycling-related crash risk and the role of cannabis and alcohol: a case-crossover study. *Preventive Medicine*, *66*, 80–6. doi:10.1016/j.ypmed.2014.06.006

Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. British Medical Journal, 344, e536.

Blows S, Ivers RQ, Connor J, Ameratunga S, Woodward M, Norton R. Marijuana use and car crash injury. Addiction 2005:100;605-11.

Barrio G, Jiménez-Mejías E, Pulido J, Lardelli-Claret P, Bravo MJ, de la Fuente L. Association between cannabis use and non-traffic injuries. Accid Anal Prev. 2012;47:172–6. doi:10.1016/j.aap.2012.01.002.

Braun, B. L., Tekawa, I. S., Gerberich, S. G., & Sidney, S. (1998). Marijuana Use and Medically Attended Injury Events. *Annals of Emergency Medicine*, *32*(3), 353–360. doi:10.1016/S0196-0644(98)70013-7

Chiolero, A., & Schmid, H. (2002). Repeated self-reported injuries and substance use among young adolescents: the case of Switzerland. *Sozial- Und Präventivmedizin, 47*(5), 289–97. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12512222

Chipman ML, Macdonald S, Mann RE. Being "at fault" in traffic crashes: Does alcohol, cannabis, cocaine, or polydrug abuse make a difference? Inj Prev 2003;9:343– 8.

Drummer OH, Gerostamoulos J, Batziris H, Chu M, Caplehorn J, Robertson MD, et al. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accid Anal Prev 2004;36:239-48.

Gerberich, S. (2003). Marijuana Use and Injury Events Resulting in Hospitalization, ,. *Annals of Epidemiology*, *13*(4), 230–237. doi:10.1016/S1047-2797(02)00411-8

Gmel G, Kuendig H, Rehm J, Schreyer N, Daeppen J-B. Alcohol and cannabis use as risk factors for injury--a case-crossover analysis in a Swiss hospital emergency department. BMC Public Health. 2009;9(1):40. doi:10.1186/1471-2458-9-40.

Hartman RL, Huestis MA. (2013). Cannabis effects on driving skills. Clin Chem.59(3):478-92.

Laumon B, Gadegbeku B, Martin J-L, Biecheler M-B, SAM Group. Cannabis intoxication and fatal road crashes in France: population based case-control study. BMJ 2005;331:1371-7.

Lowenstein, S. R. & Koziol-McLain, J. (2001). Drugs and traffic crash responsibility: A study of injured motorists in Colorado. Journal of Trauma, 50, 313-320.

Macdonald, S., Wells, S., & Lothian, S. (1998). Comparison of lifestyle and substance use factors related to accidental injuries at work, home and recreational events. *Accident; Analysis and Prevention*, *30*(1), 21–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9542541

Macdonald, S., Hall W, Roman P., Stockwell T., Coghlan M., Nesvaag S. Addiction. 2010; 105,408-416.

Mann RE, Adlaf E, Zhao J, Stoduto G, Ialomiteanu A, Smart RG, Asbridge M. Cannabis use and self-reported collisions in a representative sample of adult drivers. J Safety Res 2007;38:669 –74.Mura P, Kintz P, Ludes B, Gaulier JM, Marquet P, Martin-Dupont S, et al. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. Forensic Sci Int 2003;133:79-85.

Price JW. Marijuana and Workplace Safety: An Examination of Urine Drug Tests. Journal of Addictive Diseases. 2014; 33,24-27.

Polen, M. R., Sidney, S., Tekawa, I. S., Sadler, M., & Friedman, G. D. (1993). Health care use by frequent marijuana smokers who do not smoke tobacco. *The Western Journal of*

Medicine, 158(6), 596–601. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1311782&tool=pmcentrez&rend ertype=abstract

Pulido J, Barrio G, Lardelli P, Bravo MJ, Regidor E, De La Fuente L. Association between cannabis and cocaine use, traffic injuries and use of protective devices. Eur J Public Health 2011;21: 753–5.

Shipp EM, Tortolero SR, Cooper SP, Baumler EG, Weller NF. Substance Use and Occupational Injuries Among High School Students in South Texas. The American Journal of Drug and Alcohol Abuse. 2005; 31,253-265. .

Siwani, R., Tombers, N. M., Rieck, K. L., & Cofer, S. A. (2014). Comparative analysis of fracture characteristics of the developing mandible: the Mayo Clinic experience. *International Journal of Pediatric Otorhinolaryngology, 78*(7), 1066–70. doi:10.1016/j.ijporl.2014.04.005

Tait, R. J., Anstey, K. J., & Butterworth, P. (2010). Incidence of self-reported brain injury and the relationship with substance abuse: findings from a longitudinal community survey. *BMC Public Health, 10*(1), 171. doi:10.1186/1471-2458-10-171

Wadsworth, E. J. K., Moss, S. C., Simpson, S. a, & Smith, a P. (2006). A community based investigation of the association between cannabis use, injuries and accidents. *Journal of Psychopharmacology (Oxford, England), 20*(1), 5–13. doi:10.1177/0269881105056642

Woolard R, Nirenberg TD, Becker B, et al. Marijuana Use and Prior Injury among Injured Problem Drinkers. Acad Emerg Med. 2003;10(1):43–51.