To Vape or Not to Vape: Is That the Question?

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Electronic cigarette
An electronic cigarette, developed by a Chinese company, gives the user nicotine but no fire, no tar, no carbon monoxide, no ash and no stub.

Comparison
<table>
<thead>
<tr>
<th>One e-cigarette</th>
<th>Regular cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>6-7 cigarettes</td>
</tr>
<tr>
<td>6-24 mg.</td>
<td>15</td>
</tr>
<tr>
<td>24 mg of nicotine: 0.16 mg/puff</td>
<td>Cigarette with 1.8 mg of nicotine: 0.16 mg/puff</td>
</tr>
</tbody>
</table>

Source: E-Cig. Graphic: Ell Poll, Elisabeth Nielsen.
Evolution of E-cigarette Devices: How Many Do You Know?

One vapor unit, 59 mg nicotine/pod = >one pack of cigarettes

The smoke generated by iQOS contains substances from pyrolysis and thermogenic degradation that are identical to the constituents found in traditional tobacco cigarette smoke.

How about These?

Backpack Vaping
Cell Phone Vape
Hoodie Vaping
E-cigarettes: Thumbs Up or Down . . .

- No cancer-causing chemicals
- Healthy alternative to the real thing
- Smoke in smoke-free areas
- Cheaper alternative
- No cancer-causing tobacco
- No fire; therefore, not a fire risk
- No passive smoke to those around us
- No bitter aftertaste

E-cigs Can Help You Quit Smoking

- Cessation rates were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes
- As currently being used, e-cigarettes are associated with significantly less quitting among smokers

Kalkhoran and Glantz, 2016.
Patterns of E-cig Use Vary by Age, Gender, Race, and Ethnicity

Table 1
Sample Characteristics and E-cigarette use by Sub-Groups, CHIS 2014 (N=1,052)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Full Sample</th>
<th>E-Cigarette Use¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% or mean</td>
<td>% or mean</td>
</tr>
<tr>
<td>E-cig User (Overall)</td>
<td>No</td>
<td>930</td>
<td>89.69%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>122</td>
<td>10.31%</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>395</td>
<td>32.79%</td>
</tr>
<tr>
<td></td>
<td>Latino</td>
<td>451</td>
<td>47.00%</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>101</td>
<td>10.59%</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>105</td>
<td>9.61%</td>
</tr>
<tr>
<td>Citizenship Status</td>
<td>US Citizen</td>
<td>916</td>
<td>86.43%</td>
</tr>
<tr>
<td></td>
<td>Naturalized Citizen</td>
<td>68</td>
<td>5.32%</td>
</tr>
<tr>
<td></td>
<td>Non-Citizen</td>
<td>68</td>
<td>8.26%</td>
</tr>
<tr>
<td>Language Spoken at Home</td>
<td>Not English Only</td>
<td>551</td>
<td>50.9%</td>
</tr>
<tr>
<td></td>
<td>English Only</td>
<td>501</td>
<td>49.1%</td>
</tr>
<tr>
<td>Secondary Education</td>
<td>High School</td>
<td>591</td>
<td>55.6%</td>
</tr>
<tr>
<td></td>
<td>Not Allowed in Home</td>
<td>461</td>
<td>43.4%</td>
</tr>
<tr>
<td></td>
<td>Not Allowed by Other</td>
<td>113</td>
<td>10.6%</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>558</td>
<td>51.11%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>494</td>
<td>48.89%</td>
</tr>
<tr>
<td>Age</td>
<td>1,052</td>
<td>14.5</td>
<td>15.13</td>
</tr>
<tr>
<td>Poverty Level</td>
<td>&lt;200% FPL</td>
<td>591</td>
<td>55.6%</td>
</tr>
<tr>
<td></td>
<td>≥200% FPL</td>
<td>461</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

¹Percentages and means represent the percent of each sub-population that has ever used e-cigarettes and mean values among e-cigarette ever users.
N represents unweighted sample size

Statistics: Youth and Adolescents

- Misconception among youth that e-cigs are harmless and pose no long-term risks
- 36% of young adults (18-24) report ever using an e-cigarette; 14% report current use
- Adolescent years are important for brain development that continues to age 25
- Adolescents can get more easily addicted than adults because of increased synapse activity
  - Studies are surfacing that identify the health risks posed to young people who vape:
    - delayed brain development
    - respiratory health
    - poor impulse control, and
    - mood disorders
- Long-term health consequences of adolescent use is unknown
- Risks of second-/thirdhand exposure is still in question as well
Patterns of E-cig Use Vary by Age, Gender, Race, and Ethnicity

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Statistics: Youth and Adolescents

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<tr>
<td></td>
<td></td>
<td>N % or mean</td>
<td>% or mean P-Value</td>
</tr>
<tr>
<td>Ever-Use E-cigarette (Overall)</td>
<td>No</td>
<td>930 89.69%</td>
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<td>1.46%</td>
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<tr>
<td>Language Spoken at Home</td>
<td>Not English Only</td>
<td>501 50.3%</td>
<td>6.76% *</td>
</tr>
<tr>
<td></td>
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<td>551 49.7%</td>
<td>13.89%</td>
</tr>
<tr>
<td>Secondary Education</td>
<td>High School</td>
<td>600 59.82%</td>
<td>12.42%</td>
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<tr>
<td></td>
<td>Middle School or Lower</td>
<td>339 33.09%</td>
<td>7.40%</td>
</tr>
<tr>
<td></td>
<td>Not Attending School/Other</td>
<td>113</td>
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<td>15.13 *</td>
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</tr>
</tbody>
</table>

Percentages and means represent the percent of each sub-population that has ever used e-cigarettes and mean values among e-cigarette ever users. N represents unweighted sample size. FPL = Federal Poverty Level.

What Is in E-cigarettes?

IT'S NOT JUST "HARMLESS WATER VAPOR"

E-cigarette aerosol contains at least 10 chemicals on California’s Prop 65 list of chemicals known to cause cancer, birth defects or other reproductive harm.
7,000 Different Vape Flavors

What about Secondhand Vape?

• A main selling point of e-cigs is that they can be used anywhere because they don't produce toxic “smoke” that puts others at risk

• Experts say e-cig secondhand smoke contains a similar amount of tiny particles of heavy metals and other substances that can damage the lungs
Are E-cigarettes Less Harmful Than Regular Cigarettes?

Yes, but that doesn’t mean e-cigarettes are safe!

E-cigs: Toxicology

- E-cig studies \textit{in vivo} and \textit{in vitro} report inflammation
  - Mitogen-activated protein kinase
  - Janus tyrosine kinase/signal transducer and activator of transcription
  - Nuclear factor-κB signaling

- Immune-compromised state and increased susceptibility to microbial infections \textit{in vivo}

- Prolonged exposure to some constituents of e-cig aerosols results in inflammation, asthma, and/or COPD
**E-cig “Smoke” Is Carcinogenic**

1. Induction of DNA Damage
2. Inhibition of DNA Repair
3. Increase of Cell Mutation and Tumorigenic Transformation Susceptibility

Tang et al., 2018. *PNAS.*

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**Individual Responses Can Be Different . . .**

- The variety of responses among organisms that get the same dose of chemical is due to individual susceptibility

- Dose and individual susceptibility play roles in all situations involving chemicals, including medicines, tobacco, and caffeine

Some images have been removed from this slide.
Lack of Toxicological Studies on Susceptible Populations

- There is a known risk for e-cigarettes, as nicotine crosses the placenta and is a known developmental neurotoxicant
- About 6% of pregnant women use e-cigs alone; 8.5% are dual users of tobacco cigarettes and e-cigarettes
- Although uncertain about health effects, pregnant smokers are attracted to e-cigarettes as a harm-reduction strategy
- At present, the risk-benefit ratio of e-cigarette use during pregnancy is unknown

Opposing Governmental Viewpoints on E-cigarette Use during Pregnancy

“The evidence is already sufficient to provide appropriately cautious messages to pregnant women and women of reproductive age, as well as adolescents about the use of nicotine-containing products such as smokeless tobacco and e-cigarettes, and newer forms of nicotine-containing tobacco products, as alternatives to smoking.”

-2014 Report of the Surgeon General

“[If a woman is really struggling [to give up] and wants to use e-cigarettes, from what we know to date in the UK we should not be preventing those women from using them.”

Linda Bauld, Chair of the Smoking in Pregnancy Challenge Group
Does Early-Life Exposure to E-cigarettes, with or without Nicotine, Alter Neurodevelopment, Produce Neuroinflammation, and/or Change Adult Offspring Behavior?

Generation system developed by Gordon and Corbett, NYU.

Neuro-Related Outcomes Associated with Conventional Cigarette Smoke Exposure Early in Life

- Fetal, childhood, and adolescent exposure to cigarette smoke is associated with adverse neurocognitive outcomes, including:
  - Decreases in general intellectual ability
  - Decreases in auditory and visual learning
  - Development of conduct disorders
  - Increased hyperactivity-impulsivity behaviors
Pre- and Postnatal Exposure to E-cig Aerosols Alters Frontal Cortex Gene Expression in a Sex-Dependent Manner and in the Absence of Nicotine

Figure 1. Treatment and sex groups have both overlapping and unique genes that were significantly changed (p<0.01)

Total Significant Gene Changes per Treatment Group and Sex
- Female offspring without nicotine: 2,630
- Male offspring without nicotine: 2,615
- Female offspring with nicotine: 1,393
- Male offspring with nicotine: 152

IPA-Predicted Disease and Biological Functions in Common with Conventional Cigarette Smoke

<table>
<thead>
<tr>
<th>Function</th>
<th>Males -Nicotine</th>
<th>Males +Nicotine</th>
<th>Females -Nicotine</th>
<th>Females +Nicotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>learning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>emotional behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperactive behavior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neonatal death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>perinatal death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aerosols without Nicotine Enhanced Hippocampus Iba-1 Expression in Adult Offspring

**Iba-1 & GFAP Expression in CA1**

![Graph showing mean intensity of Iba-1 and GFAP expression in CA1.]

- Control
- +Nicotine
- -Nicotine

Mean values (N=3M & 3F) ± SEM
For each sample 3-6 slide replicates measured
*Significantly different than control p≤0.01

**Representative Images of the CA1 Region**

- Iba-1 (red), GFAP (green) and DAPI (blue)

Testing Behavior Associated with Early-Life E-cigarette Exposure

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactive Behavior, Exploratory Behavior, Activity Levels</td>
<td>Locomotor Testing</td>
</tr>
<tr>
<td>Short-Term Memory</td>
<td>Repeated Acquisition and Performance Chamber (RAPC) Testing</td>
</tr>
<tr>
<td>Long-Term Memory and Learning</td>
<td>Operant Conditioning Chamber Testing</td>
</tr>
</tbody>
</table>

In collaboration with Dr. Cory-Slechta, U of Rochester. Lautenbain et al., 2016.
Pre- and Postnatal Exposure to E-cig Aerosols with and without Nicotine

*Increased Activity in Adult (4-mo-old) Male and Female Offspring Measured as Jump Time*

![Bar graph showing significantly different jump times for female and male offspring between control, E-cig, and E-cig+Nic treatments](image)

n=10 mice/treatment group

---

Pre- and Postnatal Exposure of Mice to E-cig Aerosols with and without Nicotine

*Increased Adult (4-mo-old) Male and Female Speed of Movement (Average Velocity Time)*

![Bar graph showing significantly different average velocities for female and male offspring between control, E-cig, and E-cig+Nic treatments](image)

n=10 mice/treatment group
Study 2: E-cig Prenatal Exposure

<table>
<thead>
<tr>
<th>Behavioral Task</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FA</td>
<td>PGVG</td>
</tr>
<tr>
<td>Locomotor Activity</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety and Arousal</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Behavioral Despair (depression)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Repetitive Digging</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Learning and Memory</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

J. Schwartzer et al., In revision, EHP 2019.

Translational Take-Home Messages

- Consideration of offspring sex is an important factor for evaluating health outcomes

- The fetus and offspring from a pregnant woman using e-cigs without nicotine are as vulnerable to “vape” effects on neurodevelopment as those exposed to nicotine-based e-cigs

- Predicted adverse health outcomes (memory, learning, activity) of early-life exposure to e-cigs appear similar to those seen in offspring prenatally exposed to cigarette smoke

- Behavioral phenotypes in adult offspring are consistent with attention deficit hyperactivity disorder and anxiety disorder

- While health impacts of second-/thirdhand e-cig aerosol exposures are not clear, caution is recommended for pregnant smokers and babies living with “vapers”
**Study 2: E-cig Prenatal Exposure**

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J. Schwartzer et al., In revision, EHP 2019.

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**Vaping: Constrictive Bronchiolitis (Popcorn Lung)**

**E-cig or Vaping-Associated Lung Injury (EVALI)**

- Patients have reported symptoms such as:
  - cough, shortness of breath, or chest pain
  - nausea, vomiting, abdominal pain, or diarrhea
  - fever, chills, or weight loss
- Some patients reported symptoms over a few days; others reported symptoms developed over several weeks.
- A lung infection does not appear to be causing the symptoms.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Short-Term Effects</th>
<th>Long-Term Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metallic aftertaste</td>
<td>Periodontitis</td>
</tr>
<tr>
<td>Choking</td>
<td>Rhinitis</td>
</tr>
<tr>
<td>Coughing</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Sneezing</td>
<td>Anemia</td>
</tr>
<tr>
<td>Nausea</td>
<td>Cardiac rhythm changes</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Headache</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Seizures</td>
</tr>
<tr>
<td>Confusion</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Pneumonia</td>
</tr>
</tbody>
</table>

*Hu, Alfi, & Talbot (2013); U.S. Food and Drug Administration (2013).*
**Pulmonary Toxicity: Vaping**

"Vaping-Associated Lung Injury"

- NEJM Correspondence 10/2/2019
- Histopathology
  - New evidence to add to clinical and imaging data
  - New diagnostic clues
- Exogenous lipoid pneumonia?
  - Does the histology/imaging data thus far support this hypothesis?
- Exposure versus toxicity

**CDC (2019): Most People Who Died from Vaping-Linked Disease Used Products Containing THC**

Potential Culprits in Mystery Lung illnesses: Black-Market Vaping Products

- Some of the THC vaping cartridges seized by Minnesota law enforcement officials in a record drug arrest in Anoka County in September (AP)
- Advertising logos for cannabis brands are displayed on the side of a vape shop in downtown Los Angeles. (Richard Vogel/APos; Washington Post, 2019)
EVALI: The Search Continues

- A substance that has turned up in many THC samples is vitamin E oil

- Experts in the legal marijuana industry say it is added to THC oil to fill vape cartridges

- Legally sold vitamin E acetate is commonly used as a nutritional supplement and in skin-care products

- Health officials warn it could be hazardous when inhaled, potentially causing the sorts of symptoms many patients have reported: cough, shortness of breath, and chest pain

Toxicology: Food for Thought

- What e-cig design features alter the production of and user exposure to different toxicants, and are we using the correct parameters for our studies?

- What about the health effects of dual e-cig and tobacco users? Does e-cig use lead to nicotine addiction and the dual use of tobacco cigarettes?

- What exposure biomarkers should be used to determine e-cig toxicant exposure, disease risk, morbidity, and mortality?

- On which short- and long-term health endpoints should toxicology research focus?

- How well do toxicology studies reflect effects on vulnerable populations?

- Can toxicology studies help us move the e-cigarette health and science field forward, or can we solely rely on human studies?
Acknowledgement and Thanks

NYU Researchers
Dr. Jason Blum

Collaborators
Drs. C. Klein (NYU School of Med)
D. Cory-Slechta (U. of Rochester)
M. Aschner (Albert Einstein)
J. Schwartzer (Mt. Holyoke)

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