

Practical solutions to the problem of low quality in e-cigarette research

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I have undertaken research and consultancy for companies that develop and manufacture smoking cessation medicines; not tobacco companies or e-cigarettes companies.

Most of the research in which I am involved is funded by Cancer Research UK.

I use two examples that claim that e-cigarettes are harmful because such papers are more prevalent than ones claiming the opposite.

Low quality in e-cigarette research

Making claims that are unwarranted because of

- unwarranted extrapolation from study measures, populations or species
- making unwarranted causal inferences from study designs
- misleading use of terminology
- failing to set findings in context
- selective inclusion of studies in reviews
- double standards when judging the quality of studies
- combining studies in reviews that should not be combined

Sources of bias

- Desire for 'impact'
- Wishful thinking
- Desire for confirmation
- Not adequately offset by processes in conduct of science
 - Lack of transparency in reporting
 - Acceptance of ambiguous and misleading language
 - Inadequate scrutiny prior to publication and press coverage

Two components of the solution

Open Science

- Adoption of practices that promote transparency and accountability

Ontologies

- Ways of representing information that improve clarity and interoperability

Open science

- Greater co-operation and transparency in
 - Conducting
 - Publishing
 - Evaluating
- Leads to research that is more:
 - Robust
 - Efficient
 - Beneficial to society

Open science in practice

ADDICTION **SSA** SOCIETY FOR THE STUDY OF ADDICTION

Editorial |  Free Access |

E-cigarette research needs to adopt open science practices to improve quality

Marcus R. Munafò , Robert West

First published: 13 July 2019 | <https://doi.org/10.1111/add.14749>

‘... some or all elements of a research work-flow are made publicly available ... this includes **pre-registration of study protocols**, sharing of study materials, posting of study data’

Pre-registration



What is Preregistration?

When you preregister your research, you're simply specifying to your plan in advance, before you gather data. Preregistration separates *hypothesis-generating* (exploratory) from *hypothesis-testing* (confirmatory) research. Both are important. But the same data cannot be used to generate and test a hypothesis, which can happen unintentionally and reduce the credibility of your results. Addressing this problem through planning improves the quality and transparency of your research, helping others who may wish to build on it.

Confirmatory Research

- Hypothesis testing
- Results are held to the highest standards
- Data-independent
- Minimizes false positives
- P-values retain diagnostic value
- Inferences may be drawn to wider population

Exploratory Research

- Hypothesis generating
- Results deserve to be replicated and confirmed
- Data-dependent
- Minimizes false negatives in order to find unexpected discoveries
- P-values lose diagnostic value
- Not useful for making inferences to any wider population

Preregistration allows the researcher to make a clear distinction between both modes of research.

Why this matters

- Without pre-registration the reader cannot tell whether:
 - The stated hypothesis was the one originally tested
 - The main reported outcome was arrived at after multiple outcomes were assessed
 - Other analytical approaches were tried prior the one reported

This leads to a bias towards confirming pre-conceptions and ‘impactful’ findings

Why this matters in e-cigarette research

- It is extremely rare for studies other than RCTs to be pre-registered
- Studies typically involve multiple analyses with multiple options for outcome measures
- There is a strong pressure on researchers to draw conclusions on one side or the other of the debate about harm, gateway, or effect on smoking cessation
- Some researchers are making very strong claims from epidemiological studies while dismissing or ignoring claims that go against their position

Anatomy of a paper

Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health Bhatta DN, Glantz SA. J Am Heart Assoc. 2019 Jun 18;8:e012317. doi: 10.1161/JAHA.119.012317

Article Information

Metrics



See more details

-  Picked up by 24 news outlets
 -  Blogged by 1
 -  Tweeted by 58
 -  On 2 Facebook pages
 -  33 readers on Mendeley
- Download:** 9,950

Methods

Cross-sectional analysis of the Population Assessment of Tobacco and Health Wave 1 for association between e-cigarette use and having had and MI . [Longitudinal analysis of Population Assessment of Tobacco and Health Waves 1 and 2 for reverse causality analysis.](#) Logistic regression was performed to determine the associations between e-cigarette initiation and MI , adjusting for cigarette smoking, demographic and clinical variables.

Results

Every-day (adjusted odds ratio, 2.25, 95% CI : 1.23-4.11) and some-day (1.99, 95% CI : 1.11-3.58) e-cigarette use were independently associated with increased odds of having had an MI with a significant dose-response ($P < 0.0005$). Odds ratio for daily dual use of both products was 6.64 compared with a never cigarette smoker who never used e-cigarettes. Having had a myocardial infarction at Wave 1 did not predict e-cigarette use at Wave 2 ($P > 0.62$), **suggesting that reverse causality cannot explain the cross-sectional association between e-cigarette use and MI observed at Wave 1.**

Conclusions and clinical implication

‘Some-day and every-day e-cigarette use are associated with increased risk of having had a myocardial infarction, adjusted for combustible cigarette smoking. Effect of e-cigarettes are similar as conventional cigarette and dual use of e-cigarettes and conventional cigarettes at the same time is riskier than using either product alone.’

‘E-cigarettes should not be promoted or prescribed as a less risky alternative to combustible cigarettes’

The reality

- All the associations were only observed in the cross sectional analysis at Wave 1 on historic MIs
- The analysis of 'reverse causality' did not address any actual reverse causality at Wave 1 (this would not be possible with the study design)
- There was no significant association in the longitudinal analysis

The analysis plan did not appear to be pre-registered even though it is clearly framed as hypothesis testing and multiple analyses were performed and only the positive associations were included in the abstract

E-cigarette Ontology (E-CigO)

A way of representing knowledge that improves clarity and ‘inter-operability’

What do these terms refer to?

Gateway effect

Tobacco product

Tobacco industry funding

Vaping

E-cigarette

Cardiovascular risk parameter

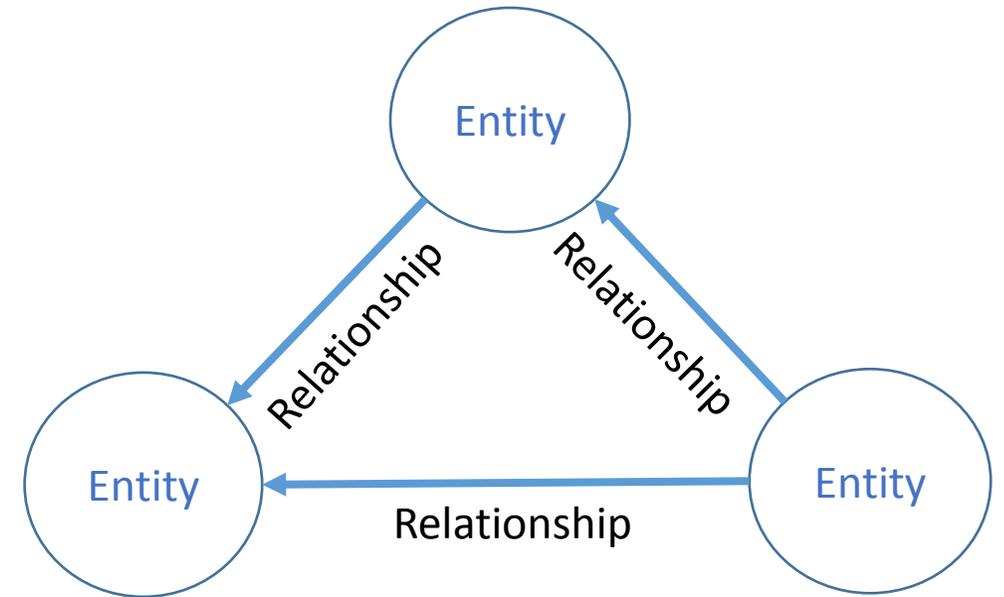
Vaping death

E-cigarette dependence

What is an ontology?

Knowledge is represented in the form of:

1. A set of unique classes or categories
2. Labels and definitions for these
3. Specification of their properties and defined relationships between them



Proof of principle

- The Gene Ontology has unified much of biological science and provided a basis for much faster knowledge accumulation



The screenshot shows the Gene Ontology website homepage. At the top left is the logo for Gene Ontology, which consists of a stylized 'go' in a circle followed by the text 'GENEONTOLOGY' and 'Unifying Biology' below it. To the right of the logo is a navigation menu with links for 'About', 'Ontology', 'Annotations', 'Downloads', and 'Help'. The main content area has a dark blue background with a faint grid pattern. The title 'THE GENE ONTOLOGY RESOURCE' is displayed in large, white, uppercase letters. Below the title, there are two paragraphs of text. The first paragraph states: 'The mission of the GO Consortium is to develop a comprehensive, **computational model of biological systems**, ranging from the molecular to the organism level, across the multiplicity of species in the tree of life.' The second paragraph states: 'The Gene Ontology (GO) knowledgebase is the world's largest source of information on the functions of genes. This knowledge is both human-readable and machine-readable, and is a foundation for computational analysis of large-scale molecular biology and genetics experiments in biomedical research.' At the bottom of the page, there is a search bar with the placeholder text 'Search GO term or Gene Product in AmiGO ...' and a green search button with a magnifying glass icon. Below the search bar, there are three radio buttons for filtering the search results: 'Any', 'Ontology', and 'Gene Product'.

GENEONTOLOGY
Unifying Biology

About Ontology Annotations Downloads Help

THE GENE ONTOLOGY RESOURCE

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Any Ontology Gene Product

Why we need E-CigO?

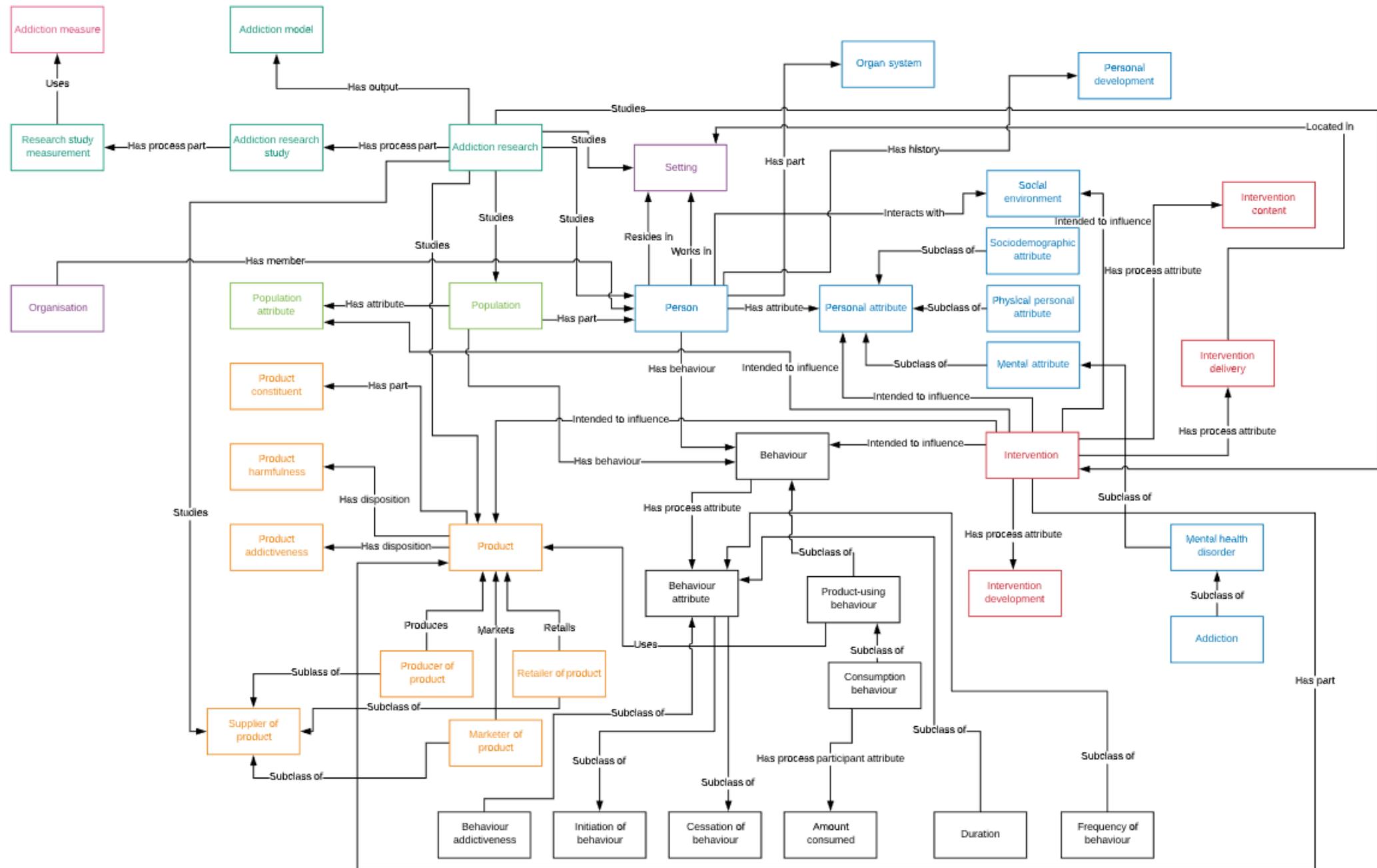
- Language being used in ways that are potentially highly misleading
- Little connection between research on either side of the debate
- Review process is not picking major errors and misleading claims
- It is proving extremely difficult and time-consuming to correct problems and studies are just being stacked up on each side
- It is proving very difficult to understand where the true research gaps are

E-CigO: Scope (part of AddictO)

Entities that are the subject of research into e-cigarettes, and the conduct of e-cigarette research

E-CigO includes entities relating to:

1. Individual people
2. Populations
3. Behaviour
4. Organisations
5. Settings
6. Products
7. Interventions
8. Research
9. Measures



Example definition

Absolute nicotine-related risk of harm

The absolute amount of risk of harm to an individual resulting from his or her use of a nicotine product in a specified amount for a specified duration in a specified way. It can be quantified in many different ways from using numeric or textual labels. No risk is represented by '0', 'Zero harm' or 'No harm'.

Example definition

E-cigarette

An electronic hand-held vaping device that produces for inhalation by a person an aerosol formed by heating a liquid, called an e-liquid. The e-liquid contains one or more humectants (propylene glycol, glycerol or glycerin), usually together with flavourants and nicotine. The heating is achieved by means of a battery-powered heating element that is activated by a switch or by suction as the user sucks on the mouthpiece of the device.

Example definition

Vaping device

A device that produces for inhalation by a person a vapour or aerosol by heating a substance that may be either liquid or solid.

Anatomy of a paper

West J Emerg Med. 2019 Aug
20;20(5):696-709. doi:
10.5811/westjem.2019.7.41661.
Nicotine Gateway Effects on
Adolescent Substance Use. Ren M,
Lotfipour S.

Nicotine Gateway Effects on Adolescent Substance Use

ARTICLES, CURRENT ISSUE: VOLUME 20 ISSUE 5, REVIEW ARTICLE, SUBSTANCE ABUSE
PUBLISHED: AUGUST 20, 2019
DOI: 10.5811/WESTJEM.2019.7.41661



Author

Affiliation

Anatomy of a paper

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Currently, the growing use of tobacco products and electronic cigarettes among teenagers represents a major public health concern. Adolescent exposure to tobacco or nicotine can lead to subsequent abuse of nicotine and other substances, which is known as the gateway hypothesis. Adolescence is a developmentally sensitive time period when risk-taking behaviors, such as sensation seeking and drug experimentation, often begin. These hallmark behaviors of adolescence are largely due to maturational changes in the brain.

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Where E-CigO could help

Promote clarity regarding

- product
- population (and species)
- disease and behavioural outcomes
- theories and models
- behaviour
- personal dispositions
- neural processes
- research methods and measures
- causal inference

Reduce

- misleading language
- inappropriate aggregation
- overgeneralisation
- muddled models
- false certainty
- ignoring relevant findings

Conclusions

- The field of e-cigarettes has revealed major weaknesses in the conduct of laboratory, clinical and population science
- The traditional approaches to research and have not been able to mitigate pressures to deliver particular findings
- **Open science practices** and development of an **E-cigarette ontology** may go some way to mitigate the problem
 - Making it easier to do high quality research and review it appropriately
 - Making it harder to exercise unconscious or conscious bias without it being evident