Indoor dust bacterial and fungal microbiota composition and allergic diseases: a scoping review to construct reusable DAG

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Major Research Project
One Health Epidemiology Microbial Agents
Institute for Risk Assessment Sciences

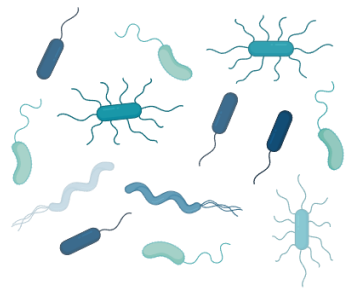
Background

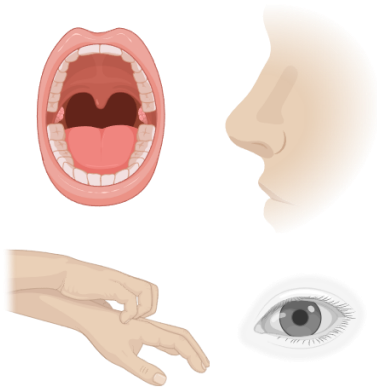
Prevalence Allergic Diseases[1]

Asthma: 3.42% (95%CI: 2.98 – 3.91)
Atopic dermatitis: 1.69% (95%CI: 1.62– 1.76)

Allergy is an exaggerated immune response against predominantly environmental or other exogenous antigens.[2]

Different microbes can promote or protect form allergies as a result of complex immunologic, genetic, and enviromental interactions.[3]





Indoor dust particles are an important source of exposure to microbes since humans spend up to 90% of their time indoors.[4]

1. Ferrari A, et al. *Lancet;* 2024; 403(10440): 2133-2161.
2. Cruz RH, et al. *Allergol Immunopathol;* 2023; 51: 16–21.
3. Kelly MS, et al. *J Allergy Clin Immunol Pract*; 2022; 10: 2206-2217.e1.
4. Shan Y, et al. *Int Microbiol* International Microbiology; 2019; 22: 297–304.

Background

Causal inference is increasingly being applied in microbiome studies

Examples

- RCT microbiota transplantation[5]
- Mendelian randomization[6]
- Mediation analysis[7]

Challenges

- No interference assumption[8]
- Consideration of interactions[9]
- Cross-sectional data[10]

5. Yu EW, et al. *PLOS Medicine.* 2020;17(3):e1003051
6. Li Z, et al. *Gastroenterology.* 2024;166(2):354-355
7. Lin L, et al. *Nature Medicine.* 2023;29(7):1750-1759
8. Hudgens, MG, et al. *J Am Stat Assoc.* 2008;103(482):832–842.
9. VanderWeele TJ. *Epidemiology.* 2014;25(5):749-61.
10. Corander J, et al. *Lancet Microbe.* 2022;3(11):e881-e887

Objectives

1. Characteristics of studies of the indoor dust microbiome
2. Study design, causal statements, and variable selection
3. Directed acyclic graph (DAG)
indoor dust microbiome → allergies

Methods

Search Strategy

- WorldCat.org and SciELO
- Keywords:

  kw:(dust) AND kw:(indoor OR dwelling OR house OR household OR residence OR store OR mall OR hospital OR workplace OR office OR school OR university OR sport OR closed environment) AND kw:(microbiota OR microbiome OR microbial community OR virome)

- initial (08-03-2023), updated: 15-09-2023 and 30-01-2024
- English and Spanish
- 2000-2024

Data extraction

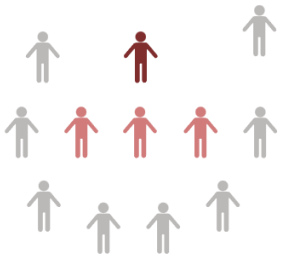
Country

Microbiome type

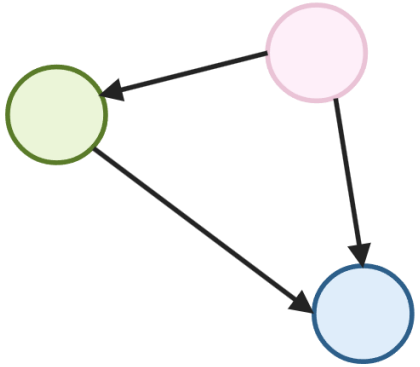
Environmental determinants

Indoor environment

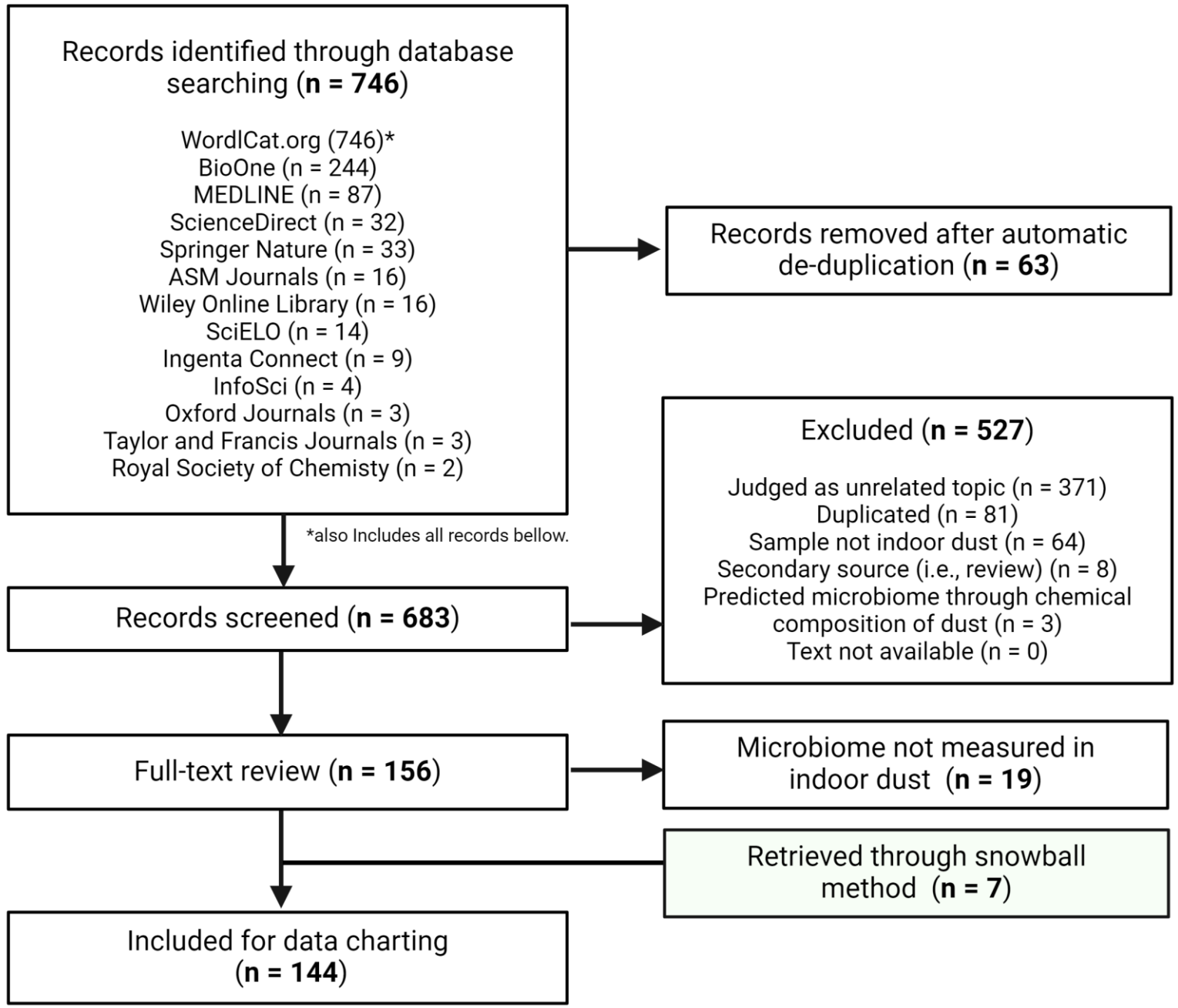
Sample collection method



Study Design

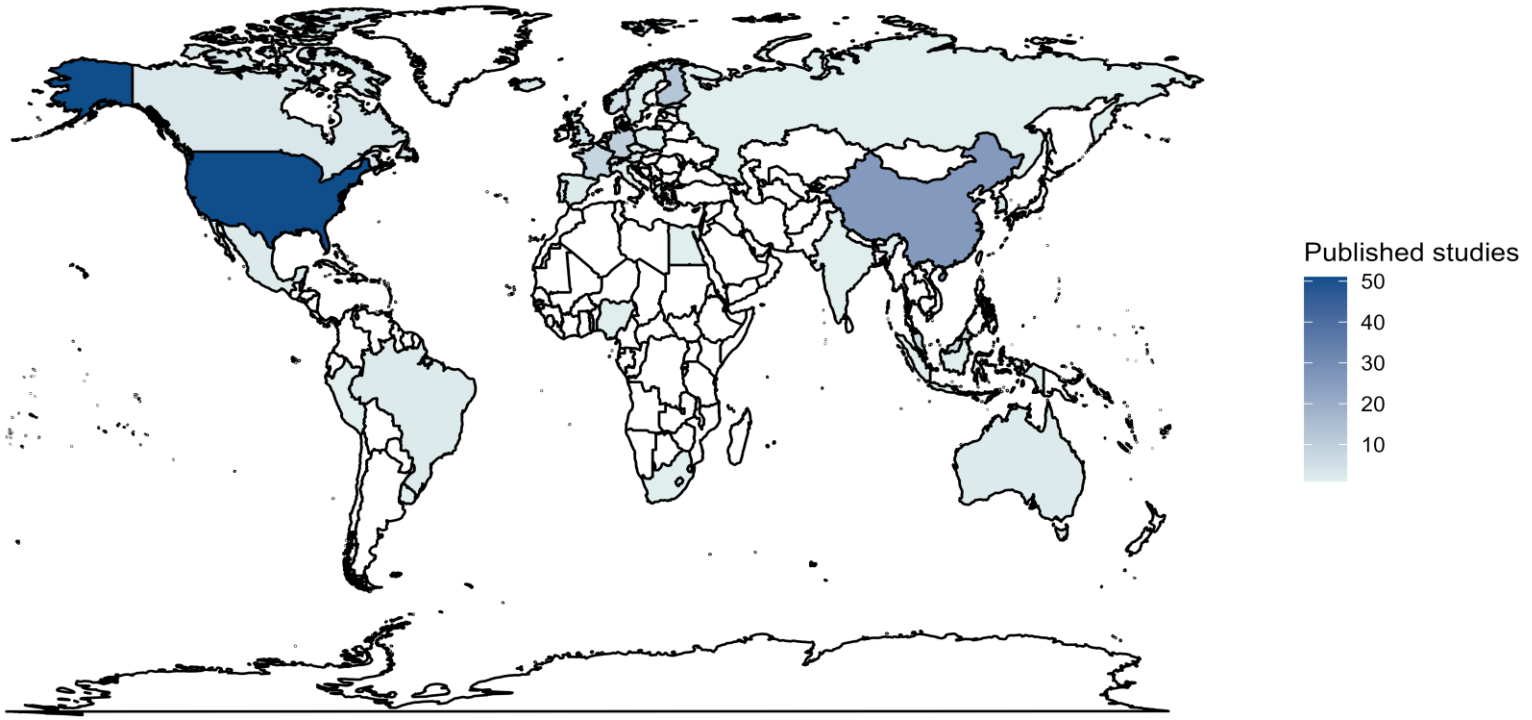


Causal statements and variable selection


Records identified through database searching (n = 746)
WordlCat.org (746)*
BioOne (n = 244)
MEDLINE (n = 87)
ScienceDirect (n = 32)
Springer Nature (n = 33)
ASM Journals (n = 16)
Wiley Online Library (n = 16)
SciELO (n = 14)
Ingenta Connect (n = 9)
InfoSci (n = 4)
Oxford Journals (n = 3)
Taylor and Francis Journals (n = 3)
Royal Society of Chemisty (n = 2)
*also Includes all records bellow.
Records removed after automatic de-duplication (n = 63)
Records screened (n = 683)
Excluded (n = 527)
Judged as unrelated topic (n = 371)
Duplicated (n = 81)
Sample not indoor dust (n = 64)
Secondary source (i.e., review) (n = 8)
Predicted microbiome through chemical composition of dust (n = 3)
Text not available (n = 0)
Full-text review (n = 156)
Microbiome not measured in indoor dust (n = 19)
Retrieved through snowball method (n = 7)
Included for data charting (n = 144)

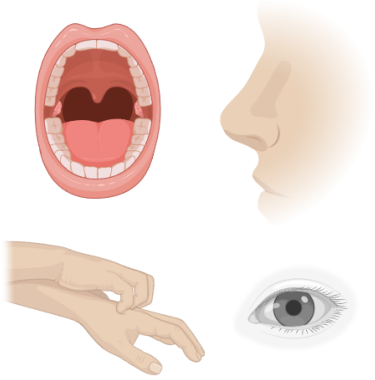
World region	n	%
Europe & Central Asia	70	40.0
North America	54	30.9
East Asia & Pacific	41	23.4
Latin America & Caribbean	6	3.4
Sub-Saharan Africa	2	1.1
Middle East & North Africa	1	0.6
South Asia	1	0.7

Indoor dust microbiome research articles per country



Income	n	%
High	131	74.9
Upper-middle	40	22.9
Lower-middle	4	2.3
Low	0	0%

Topics

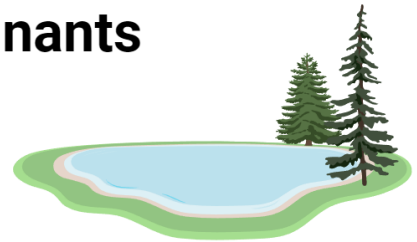


Allergies

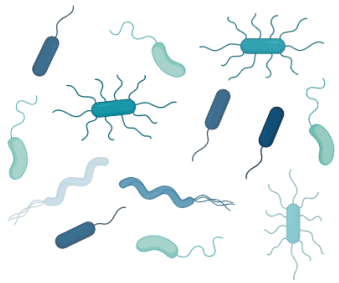
28.5% (n = 41)

Environmental Determinants

80.6% (n = 116)



Microbiome type

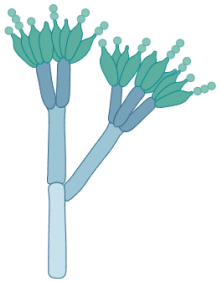


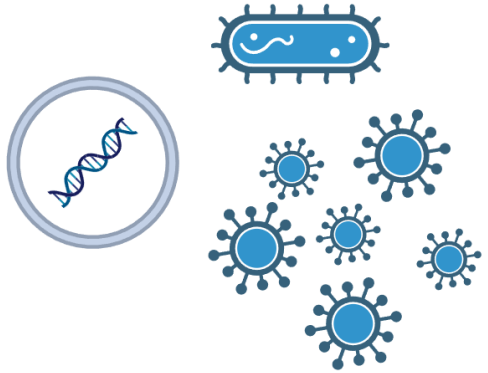
Bacterial

88.9% (n = 128)

Fungal

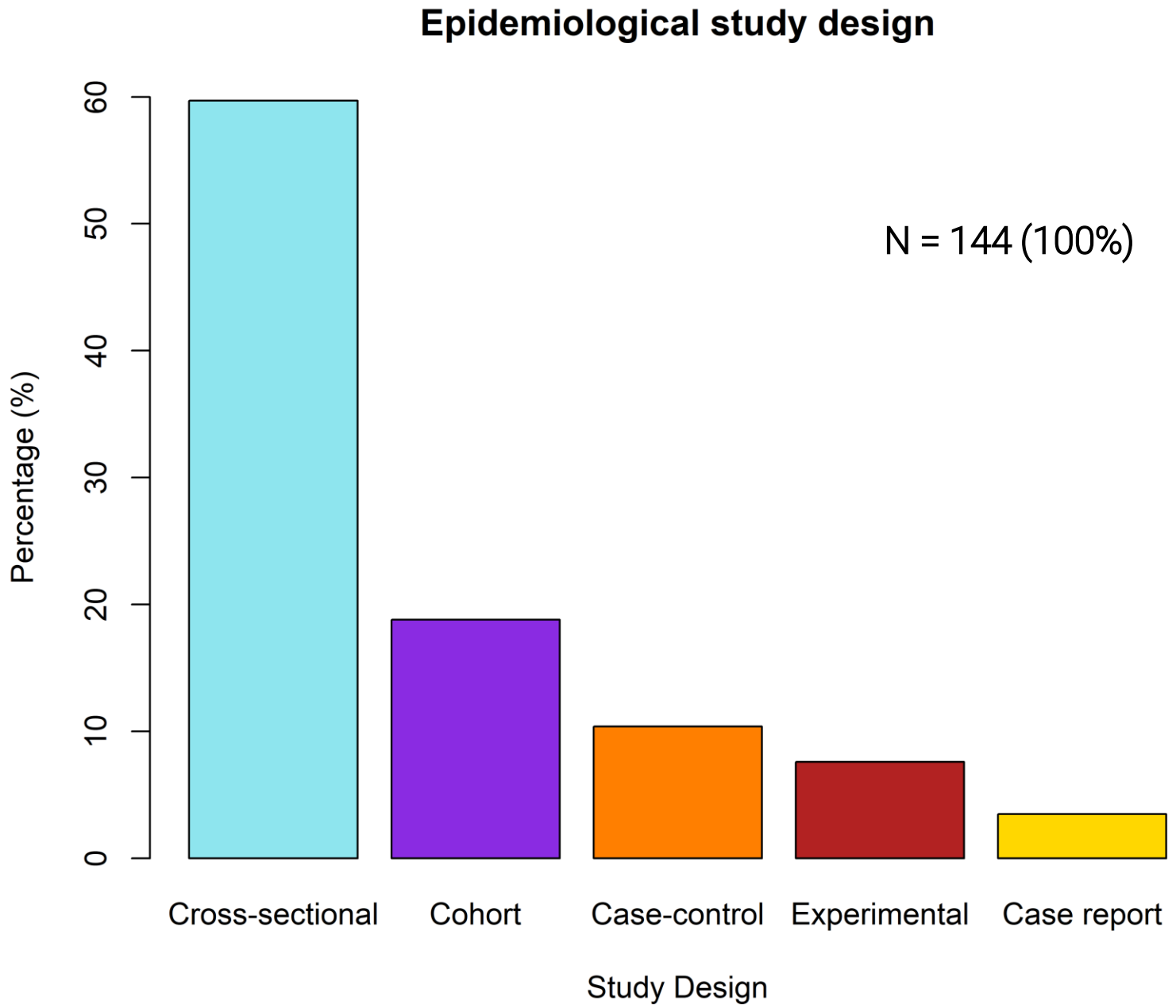
57.6% (n = 83)





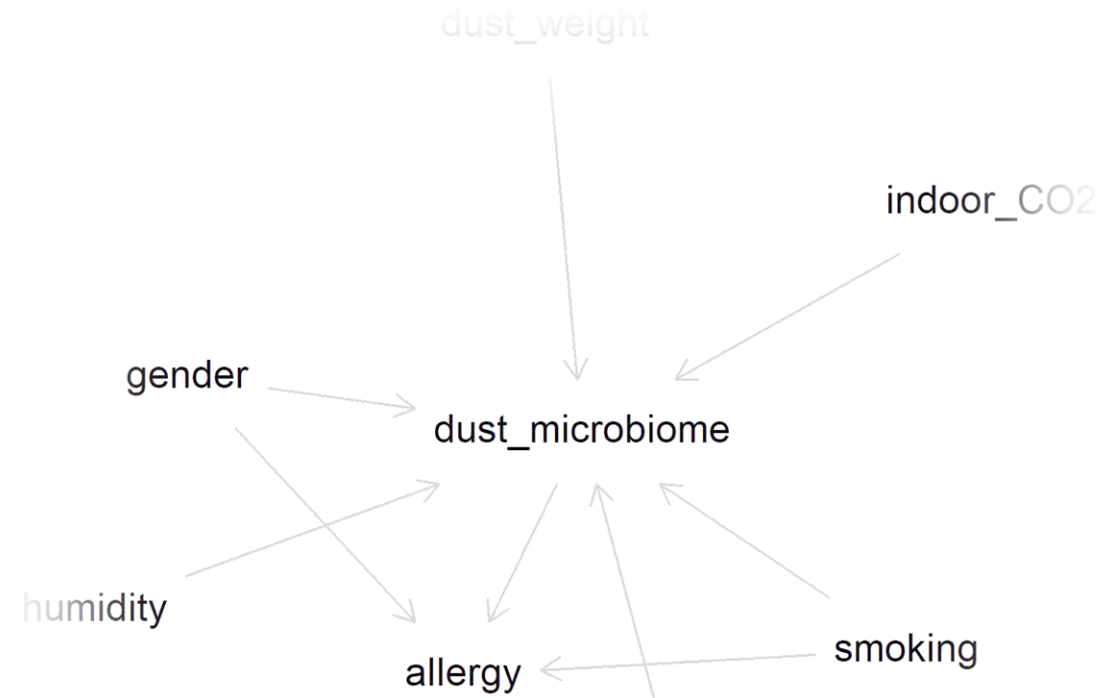
Other

6.9% (n = 10)


Epidemiological study design
Percentage (%)
0
10
20
30
40
50
60
N = 144 (100%)
Cross-sectional
Cohort
Case-control
Experimental
Case report
Study Design

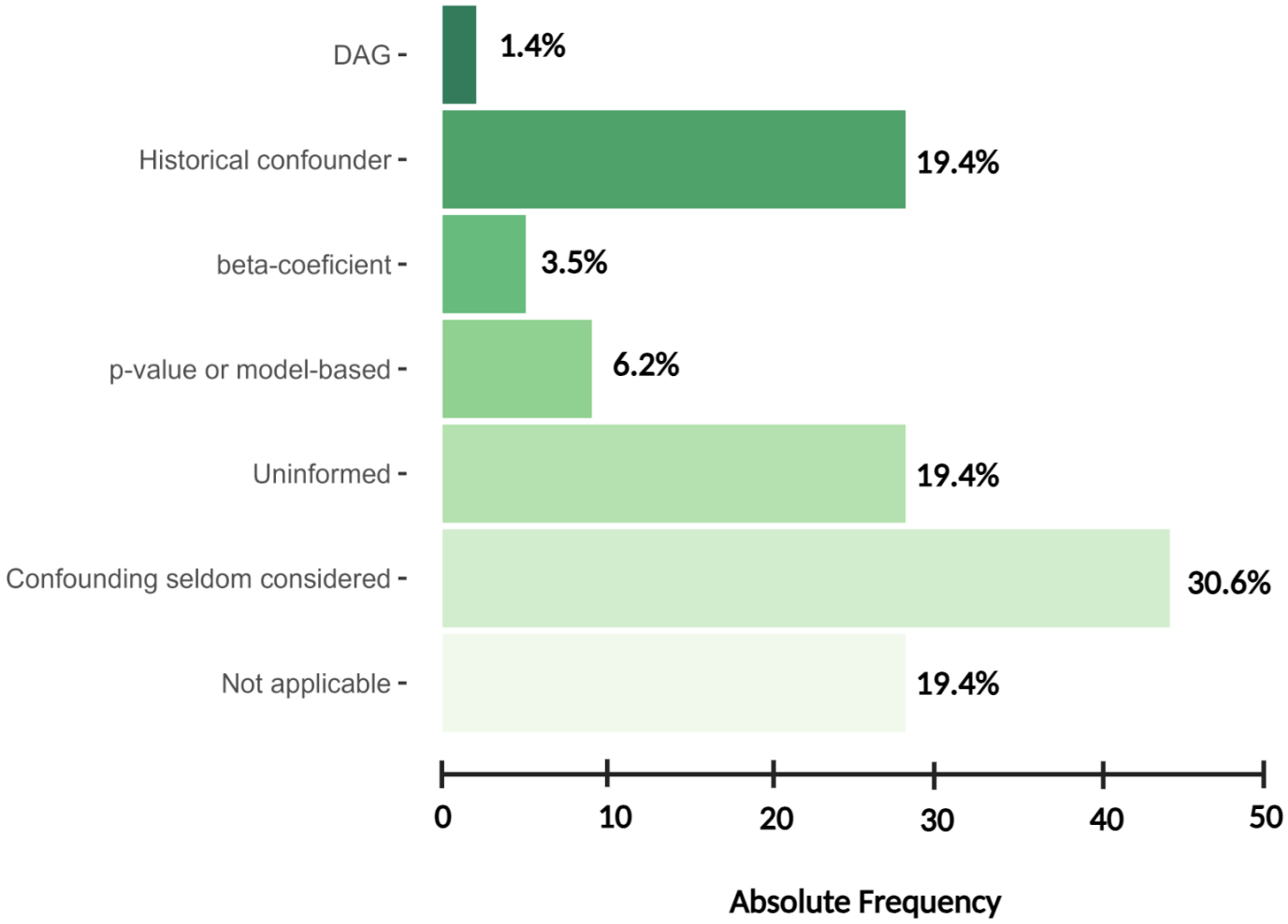
Discussion and Conclusions (Part 1)

- Research efforts have been focused in high and upper-middle income countries of three out of seven world regions.
- Environmental determinants (80.6%) and allergies (28.5%) have been recurrent topics.
- Most studies have assessed the bacterial dust microbiome, followed by fungal microbiome. The indoor dust virome remains understudied.
- Cross-sectional is the most common epidemiological study design (~60%)



Causal statements were made in 81.9% (n = 118) of studies

Method for selecting and accounting for confounding variables



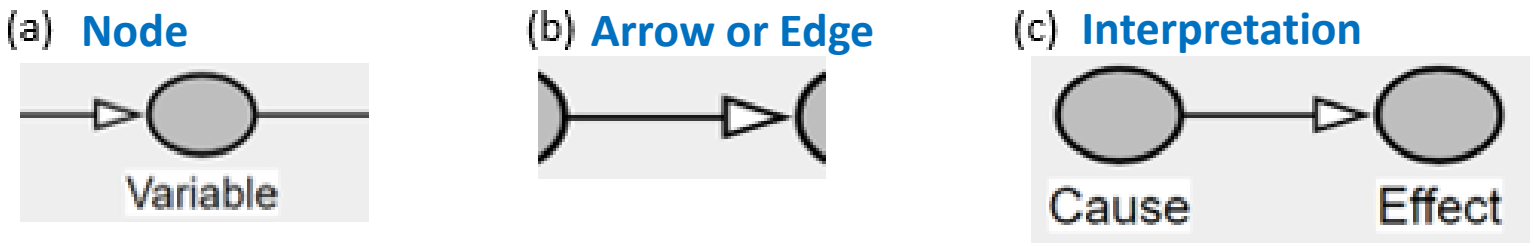
Lederer DJ, et al. *Annals of the American Thoracic Society* 2019;16(1);22-28

Constructing and documenting a reusable Directed Acyclic Graph (DAG)

dust microbiome $\rightarrow$ *allergy*

Directed Acyclic Graphs

Directed acyclic graphs (DAGs) posit causal relationships between variables as arrows between nodes.

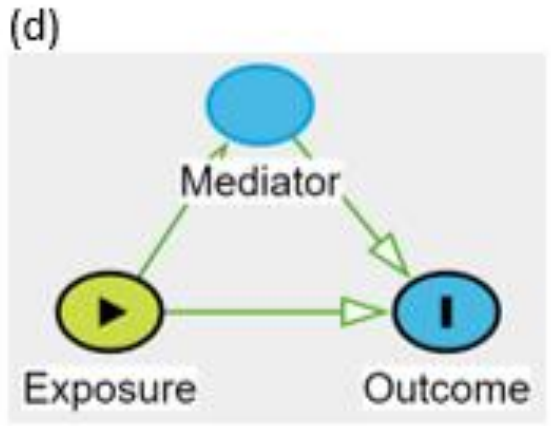


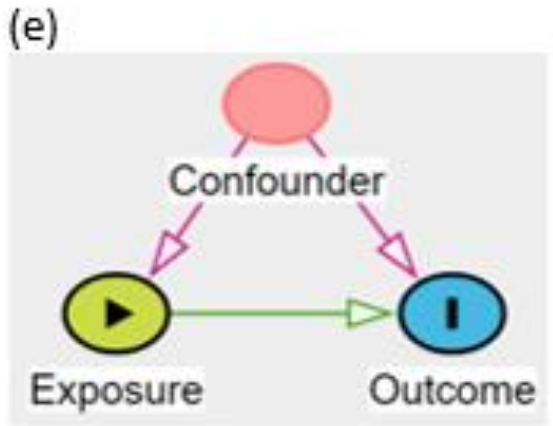
- Directed means that arrows (edges) can only be unidirectional
- Acyclic means that no combination of arrows may constitute a loop

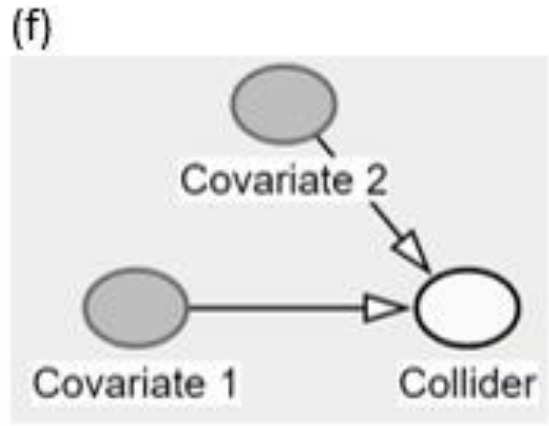
Ferguson KD, et al. *International Journal of Epidemiology* 2020;49;322-29

Directed Acyclic Graphs

DAGs are valuable tools for study design and guiding analysis.







https://dagitty.net/dags.html

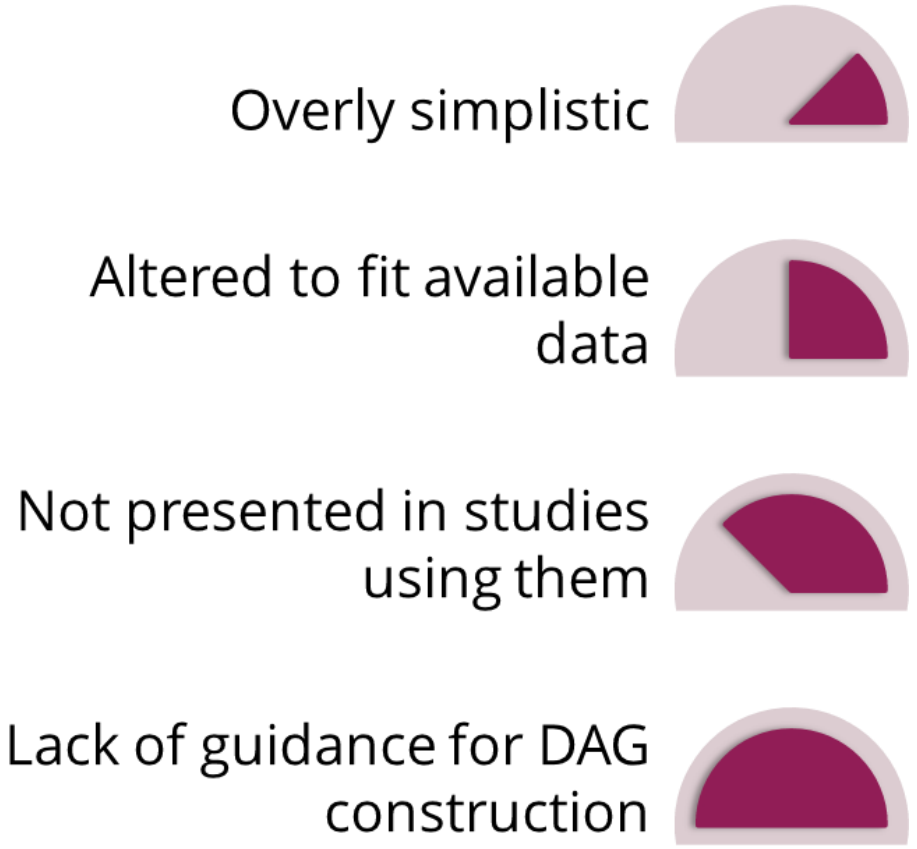
Ferguson KD, et al. *International Journal of Epidemiology* 2020;49;322-29

Directed Acyclic Graphs

- Any variable that influences at least two others should be included.
- Absence of an arrow between nodes indicates no causal effect.
- Researchers should 'work backwards' from a 'saturated' DAG—one in which all variables are inter-connected—and only delete connections that are thought impossible.

Ferguson KD, et al. *International Journal of Epidemiology* 2020;49;322-29

Problems with DAGs



Ferguson KD, et al. *International Journal of Epidemiology* 2020;49;322-29

ESC-DAG protocol

Evidence Synthesis for Constructing DAGs

Literature Search

- **Ideally** novel systematic review or review of SRs
- Well defined PICO/PECO question

Mapping

- Produce a DAG representing the conclusions of each individual study

Translation

- Assess causal characteristics of each connection

Integration

- Synthesis: Combine DAGs into one
- Recombination: Combine nodes for practical or substantive reasons

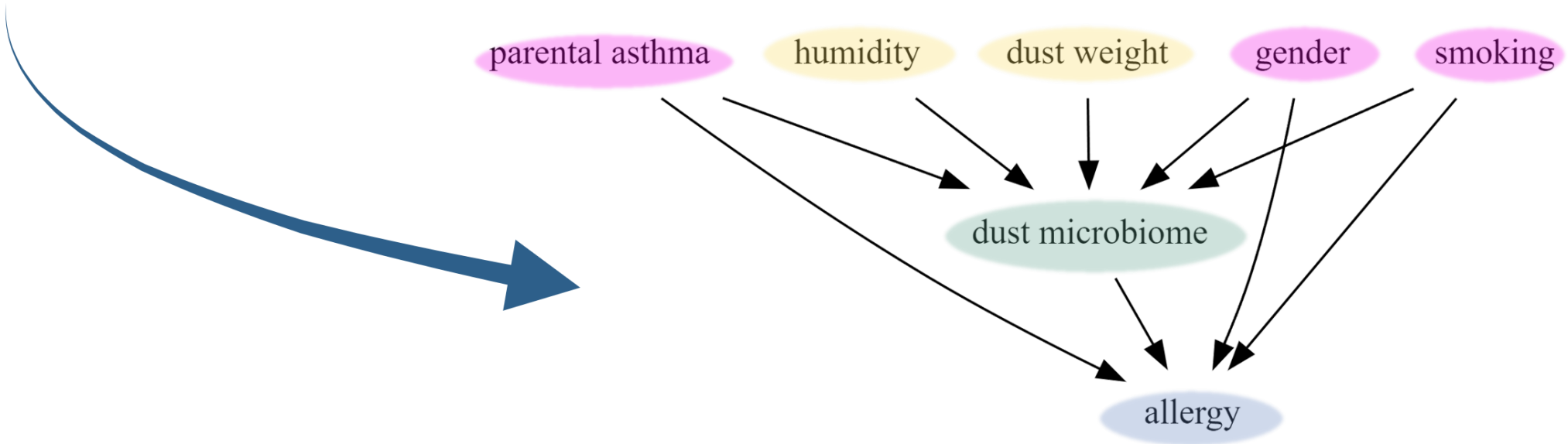
Ferguson KD, et al. *International Journal of Epidemiology* 2020;49;322-29

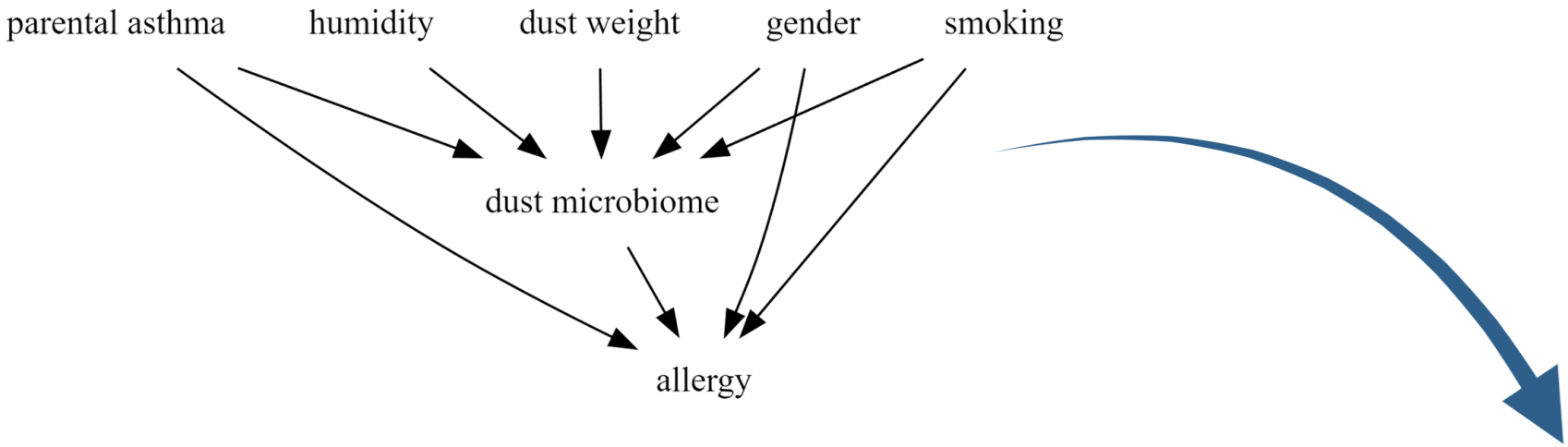
Mapping

23 studies selected
- Exposure: indoor dust microbiome
- Outcome: any allergy

Num 1 (Fu et al., 2023)

- Exposure: microbial richness/concentration
- Outcome: allergic rhinitis / non-allergic rhinitis symptoms
- Control variables: **gender**, current **smoking**, and **parental asthma**
- Other: Effect of **relative humidity** and **dust weight** on rhinitis symptoms is concluded to be *mediated* through the microbiome.



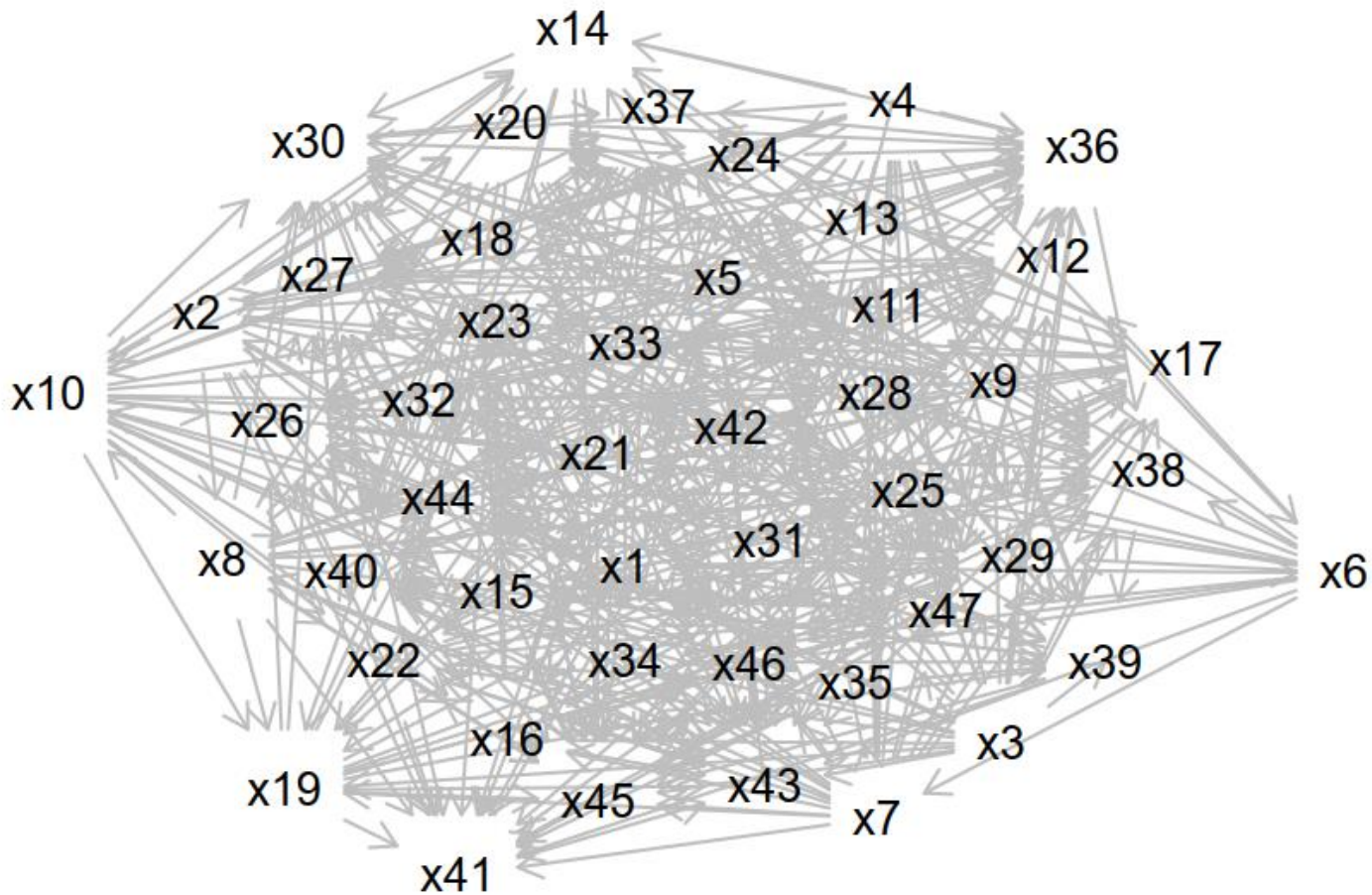


Num	Edge	Explanation
1	dust_microbiome -> allergy	main
1	dust_weight -> dust_microbiome	microbiome mediates the effect of dust weight on allergies
1	gender -> allergy	adjusted for gender
1	gender -> dust_microbiome	adjusted for gender
1	humidity -> dust_microbiome	microbiome mediates the effect of humidity on allergies
1	parental_asthma -> allergy	adjusted for parental_asthma
1	parental_asthma -> dust_microbiome	adjusted for parental_asthma
1	smoking -> allergy	adjusted for smoking
1	smoking -> dust_microbiome	adjusted for smoking

Current Status

- So far, I have assessed 13 out of the 23 studies included for the mapping stage of the ESC-DAG.
- This produced a total of 140 edges. The number of edges after de-duplication is 80.
- The number of variables (nodes) present is 47.
- If I were to only assess relationships between every variable with the exposure and outcome, ignoring all relationships between covariates, I would need to assess 90 edges.

How many edges would I need to assess to produce a saturated DAG?



This hypothetical DAG with the same number of variables contains **547** edges that I would need to assess individually.

Discussion and Conclusions (Part 2)

- Evidence synthesis construction of DAGs remains challenging and with technical limitations.
- Papers citing this method are using it in multiple deviating ways. Only few exceptional compliances, including NASA.[11]
- Authors of ESC-DAG attempted to construct a DAG with their own method and reported multiple logistical and technical limitations; dagitty website crashes with >30 nodes (variables).[12]
- Documentation and openness of ESC-DAGs has not been good. In my approach I am investing additional efforts on it.

11. Antonsen E, et al. npj Microgravity. 2024;19;10(1):32.
12. Campbell T, et al. 2021 PsyArXiv. osf.io/preprints/psyarxiv/sfp4x

Discussion and Conclusions (Part 2)

- ESC-DAGs challenge traditional epidemiologists' conceptions of DAGs.
- Current utility limited to one research question. Naive to expect researchers to follow method for every study
- Indoor dust microbiome DAGs will remain limited if there is a lag in flow of basic knowledge.
- Causal questions of *mediation* in the indoor dust microbiome field anticipated to be of special interest. Documented, reusable, and adaptable DAGs could inform the design and analysis of such studies.

Future work and perspectives

- For my own DAG, I must decide how to approach number of edges to assess in the *synthesis* phase
- Develop a resource to integrate good documentation with easiness of use. Again, documentation and open practices of ESC-DAG development need to improve.
- Future uses of robust and reproducible DAGs could resemble applications in commerce (i.e., Amazon) or NASA risk prevention

Utrecht University

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