# Oral health and markers of brain health in healthy middle-aged adults

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# Content

1. Importance of Oral Health Knowledge for Healthcare Practitioners
2. Neuroimaging markers of brain health
3. Introduction to Mendelian Randomization
4. Our study: Exploring the Link Between Oral Health and Brain Health
5. Pathophysiological hypotheses
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# Introduction: what is oral health?

- Although definitions vary, in our context, oral health refers to the absence of:
    - Periodontal disease (gum disease)
        - Gingivitis (gum inflammation)
        - Periodontitis (inflammation of inner gum and bone)
    - Caries (= cavities = decayed teeth)
        - Filled teeth
    - Tooth loss
        - Dentures

# Introduction: why is oral health important?

Oral health has implications beyond the oral cavity.

The systemic consequences of poor oral health are numerous.

The New York Times

## Why Oral Hygiene Is Crucial to Your Overall Health

Gum disease has been associated with a range of health conditions, including diabetes, heart disease, dementia and more. Here's what experts say you can do to manage the risk.

# Introduction: systemic implications of oral health

1. Diabetes
    1. Poor oral health exacerbates diabetes
    2. Poor glycemic control worsens oral health (increases oral candidiasis, bacteria shift leading to periodontal disease)

2. Periodontal disease and shifts in the oral microbiota are associated with cardiovascular diseases:
    1. Coronary artery disease
    2. Heart Failure
    3. Atrial Fibrillation
    4. Peripheral artery disease

*Diabetes Res Clin Pract. 2019 Nov:157:107839.*
*Heart Lung Circ. 2018 Nov;27(11):1327-1334*
*Circulation. 2012;125:2520-2544*

# Introduction: systemic implications of oral health

3. Pregnancy outcomes:
    1. Preterm birth
    2. Low birth weight
    3. Preeclampsia
4. Respiratory diseases:
    1. Pneumonia
5. Frailty
6. Rheumatoid arthritis
7. Kidney disease
8. Cancer

*JDR Clin Trans Res. 2018 Jan; 3(1): 10-27*
*Curr Osteoporos Rep. 2016 Dec; 14(6): 284-291*
*Front Oral Health. 2021; 2: 801815.*

# POLL QUESTION 1

# Introduction: neurological implications of oral health

1. Periodontitis and tooth loss are linked to a higher risk of:
    1. Stroke
        1. Strong association with ischemic stroke
    2. Cognitive decline
        1. In MCI patients, those with periodontitis suffer a greater cognitive decline compared to those without
    3. Dementia
        1. Periodontitis and tooth loss are risk factors for dementia.
        2. Periodontal pathogens are associated with the development of Alzheimer's disease

*Vasc Health Risk Manag. 2019;15:519-532*
*J Am Geriatr Soc. 2022;70(9):2695-2709.*
*PLoS One 2016 Mar 10;11(3):e0151081*

# Limitations of previous studies

Observational studies have important limitations:

- Unable to claim causality
- Susceptible to confounding
  - This is particularly relevant as oral health and the mentioned conditions share common risk factors:
    - Age, Smoking, Alcohol, Diet, Physical Activity, Obesity, Diabetes, Hypertension
- Reverse causation is a concern
  - Cognitive decline begins years before clinical diagnosis → may lead to deteriorating oral health habits

# Rationale for our study

1. Instead of considering clinically evident outcomes, we will consider brain MRI markers of silent brain health decline.
    1. These markers enable the measurement of silent cerebrovascular disease.
    2. They are strongly associated with the development of dementia and stroke.
    3. Their appearance and progression precede the onset of stroke/dementia by many years.
    4. They will allow us to:
        1. Minimize the risk of reverse causation.
        2. Provide stronger pathophysiological evidence.

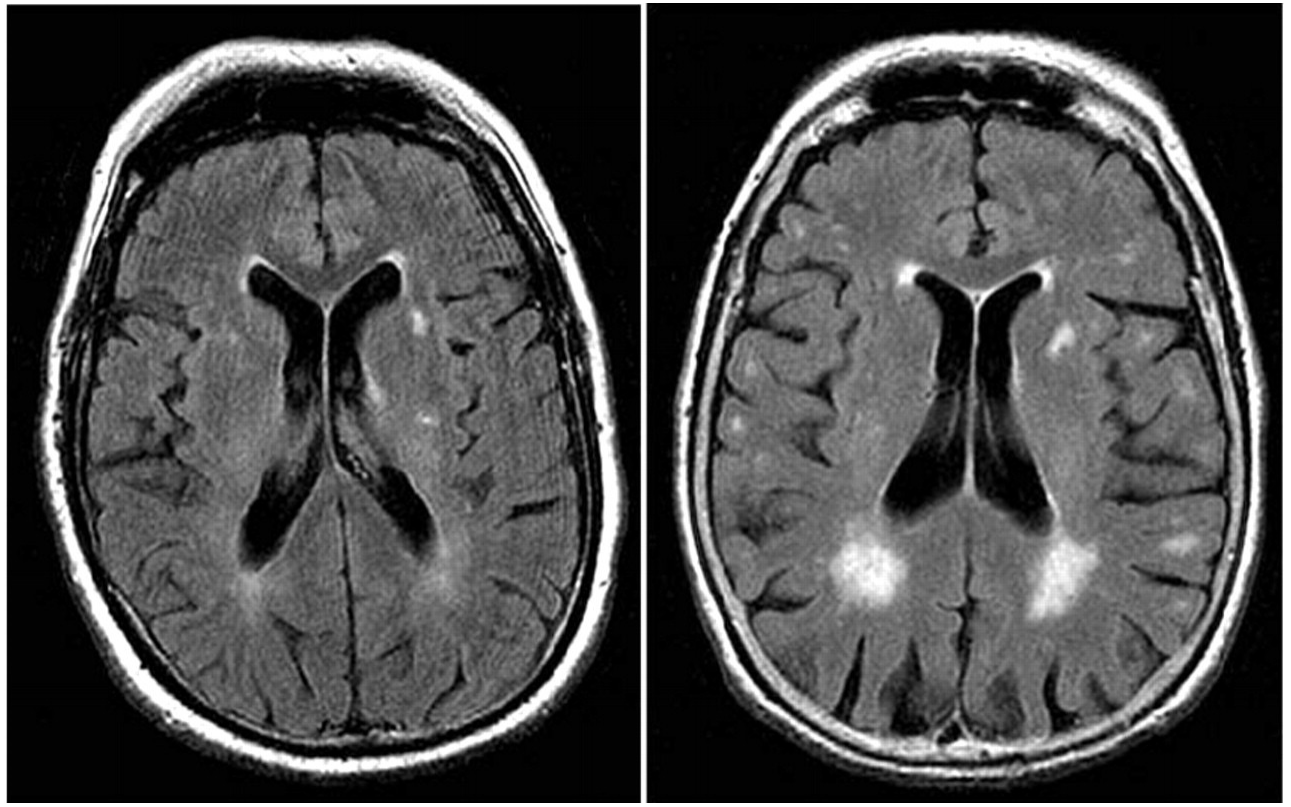
2. Instead of solely relying on a pure observational study, we will also conduct genetic analyses (Mendelian Randomization).
    1. This method enables us to suggest causation.

*Rivier et al. Neurology 2023. In press*

# Neuroimaging markers of brain health

White Matter Hyperintensities

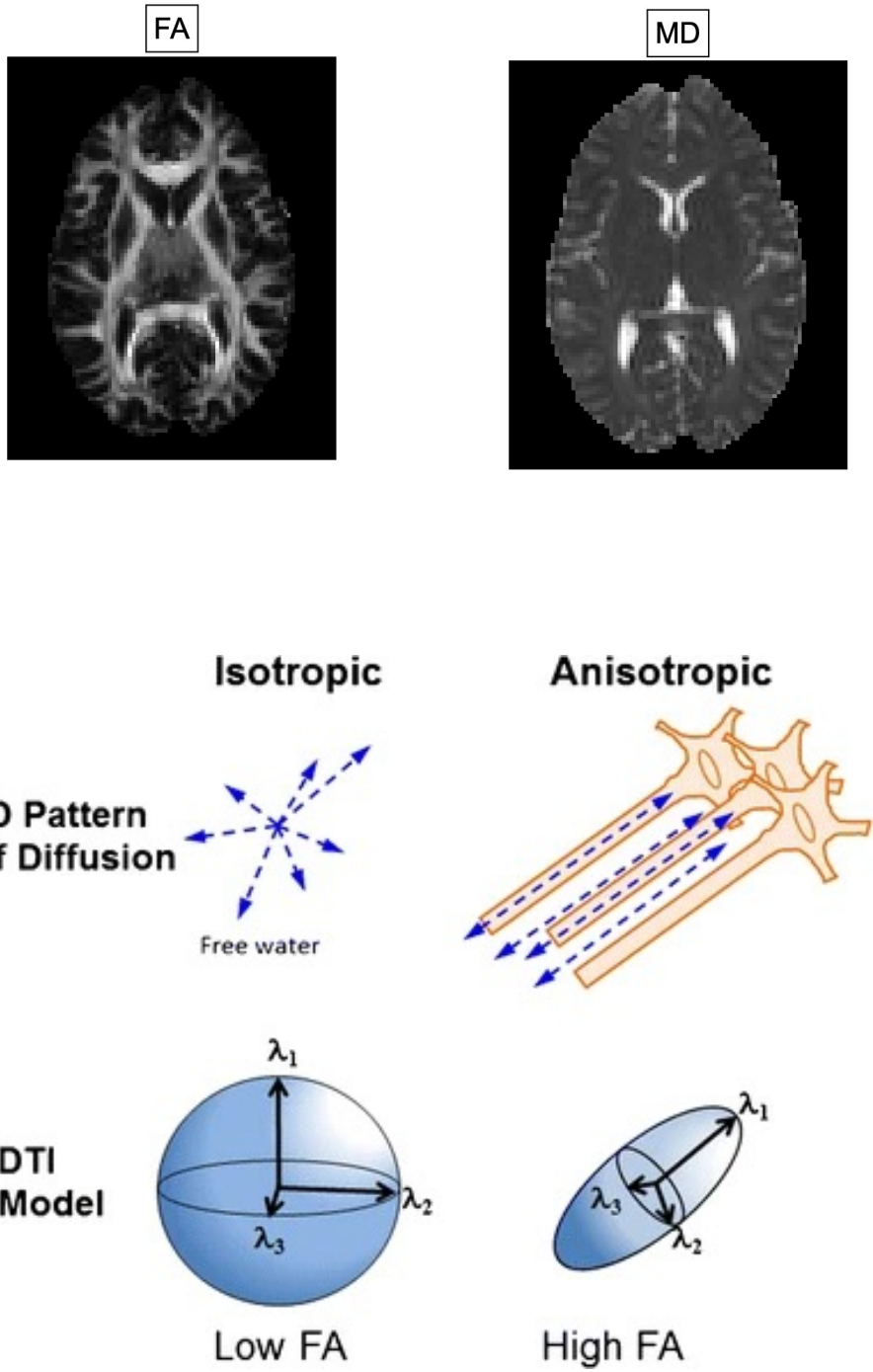
- Hyperintense spots on MRI sequences
- Found in 10-20% of individuals at 60 years of age and up to 100% of individuals at 90 years of age.
- Result from cerebral small vessel disease: ischemia, micro-hemorrhages, blood vessel walls damage
- Their presence and volume are associated and precede by many years the onset of:
  - Cognitive and functional impairments
  - Stroke
  - Dementia



# Neuroimaging markers of brain health

Fractional Anisotropy (FA) and Mean Diffusivity (MD)

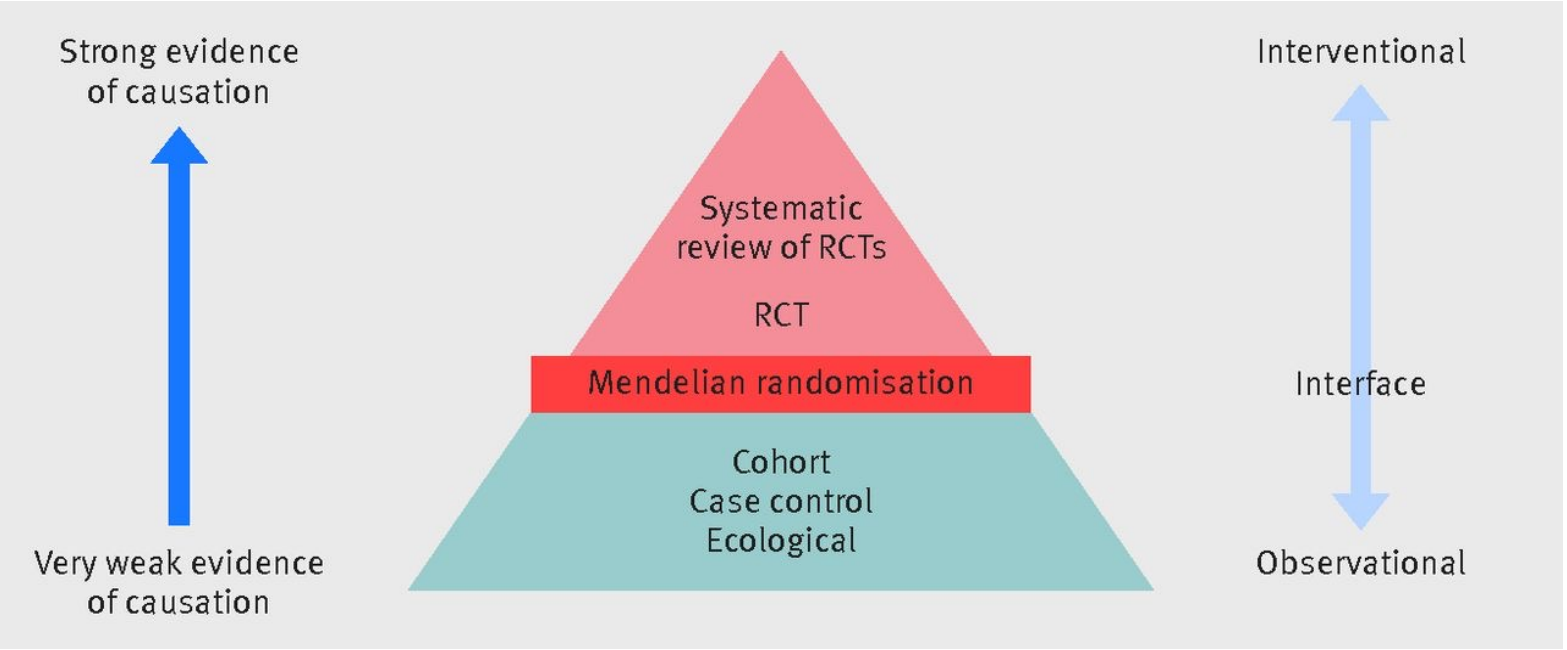
- Obtained from Diffusion Tensor Imaging (DTI) to assess white matter tracts
- Measures of the directional coherence of water diffusion
- Indicators of white matter microstructural integrity
- Informative of pathological changes in white matter
- Are associated with and precede the onset of:
  - Alzheimer's disease
  - Stroke
  - Multiple Sclerosis



# Introduction to Mendelian Randomization: Causal inference

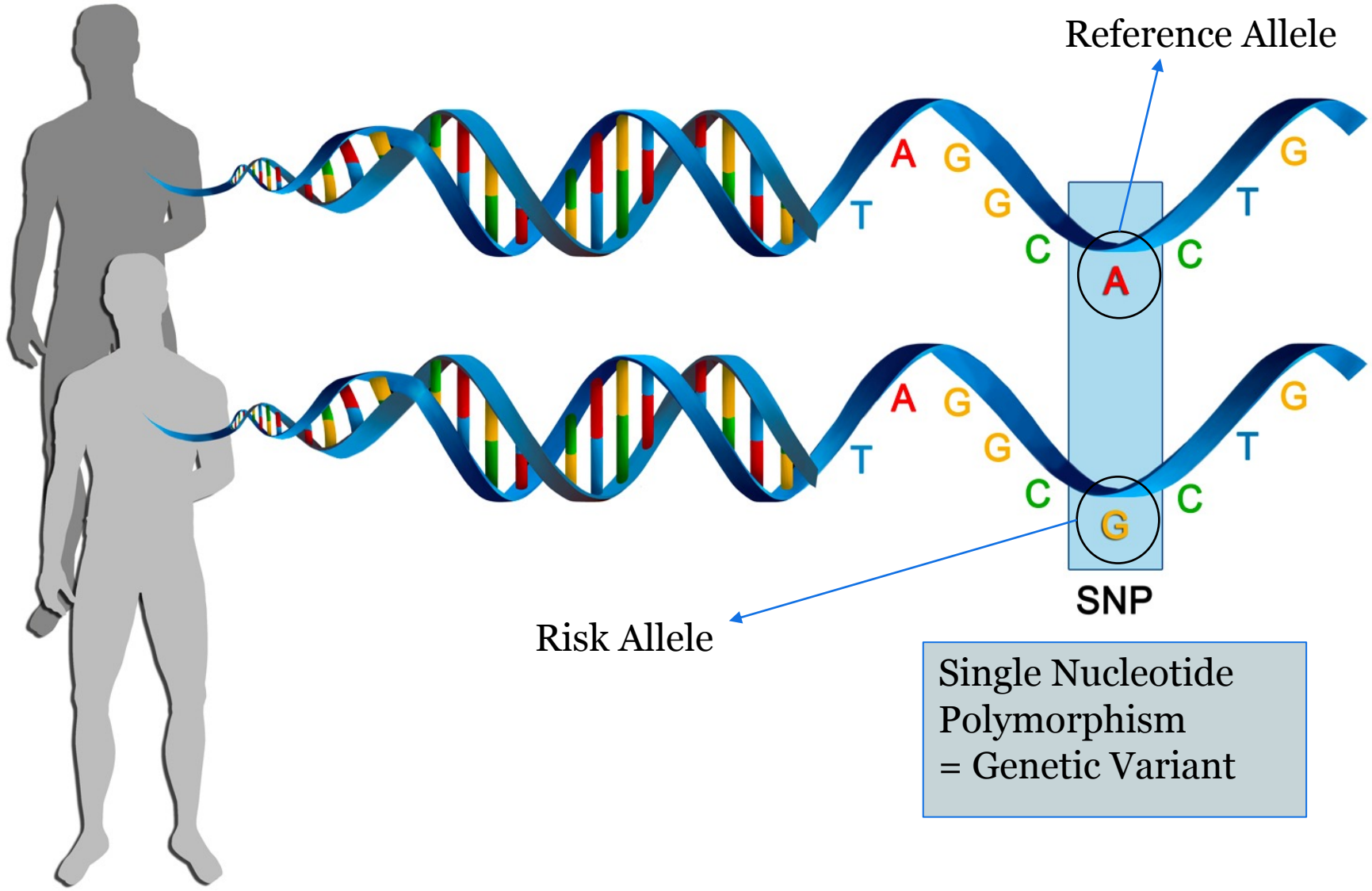
Randomized Controlled Trials are the gold standard to assess causal inference, yet they are costly and require extensive logistics.

Population genetics offers a tool to test for causation: Mendelian Randomization

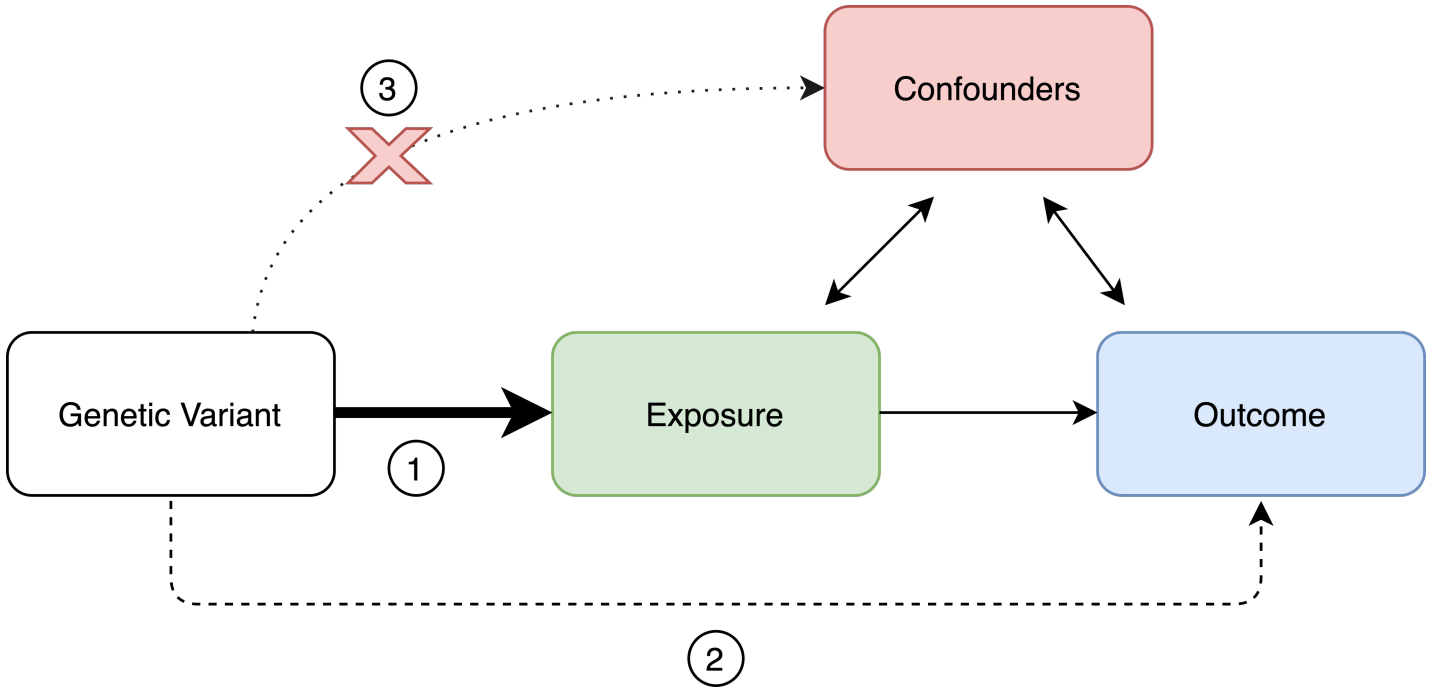


# POLL QUESTION 2

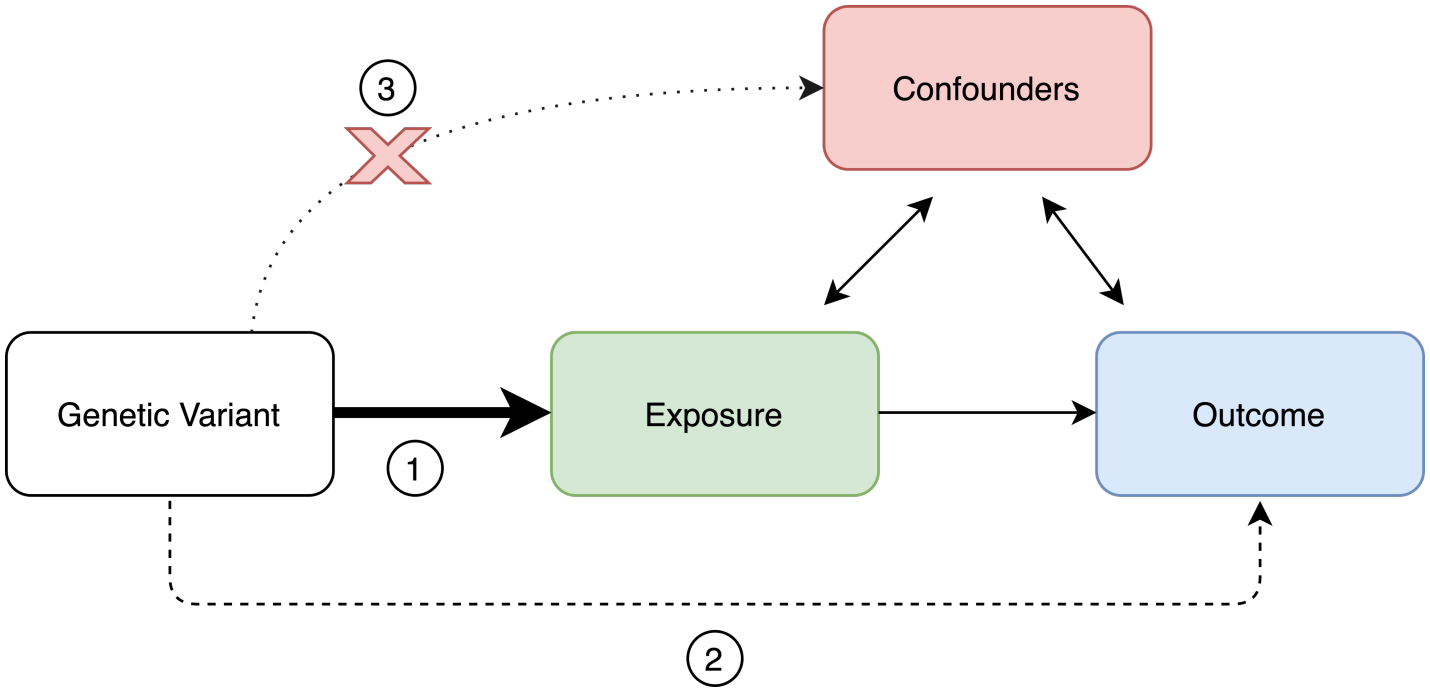
# Genetic variants - SNP



# MR is a type of instrumental variable analysis

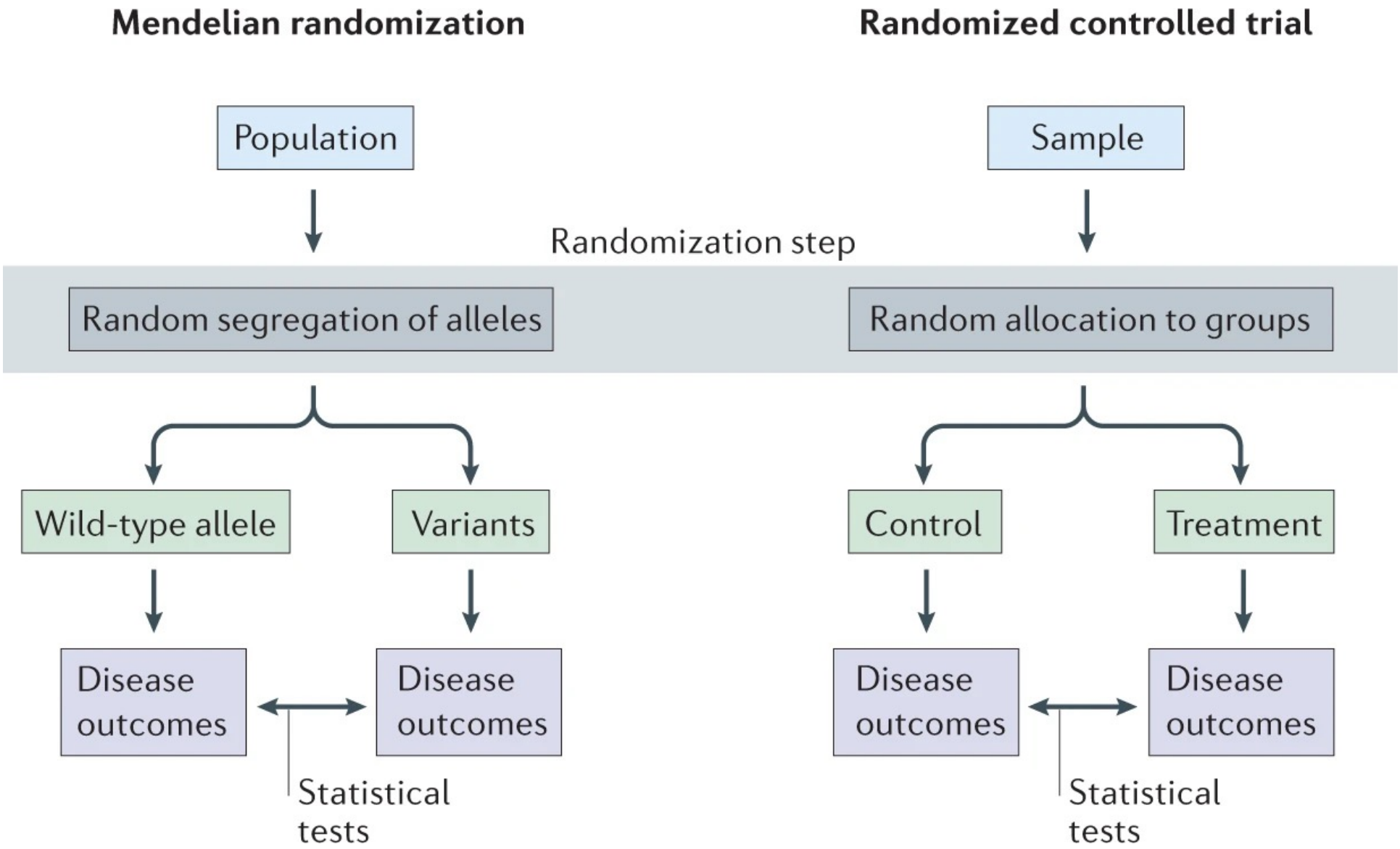


# MR is a type of instrumental variable analysis




1. Genetic variant (instrument) is strongly associated with the exposure.
2. Genetic variant (instrument) is only associated with the outcome via the exposure.
3. Genetic variant (instrument) is not associated with confounders that affect both the exposure and the outcome.

# Mendelian randomization as a genetic RCT




*Nature reviews, 2022 Sanderson*

# Question and hypothesis of our study

- Question:
  - Whether poor oral health leads to worse neuroimaging brain health profiles in healthy individuals?

- Hypothesis:
  - Poor oral health leads to detrimental brain health effects many years before the onset of dementia or stroke

# Methods: Design

- **Study design:** two-stage neuroimaging study in the UK Biobank
  1. Observational part: cross-sectional analysis
  2. Genetic part: Mendelian Randomization analyses

- **Setting: The UK Biobank**
  - Population-based cohort study
    - 500,000 community-dwelling volunteers across the United Kingdom
  - Recruitment between 2006 and 2010
  - Neuroimaging assessment between 2014 and 2016
    - 40,000 participants with research brain MRI
  - Participants are followed in time with extraction of EHR records
  - Exclusion of participants with a prior history of stroke or dementia



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# Methods: Observational study

- **Exposure: clinically defined poor oral health**
  - Loose teeth
  - Dentures
  - (Bleeding gums)
  - (Painful gums)

- **Outcome:** Neuroimaging markers:
  1. White Matter Hyperintensities (WMH) volume: log-transformation
  2. Fractional Anisotropy (FA):
     - 1st principal component over 48 brain regions
  3. Mean Diffusivity (MD):
     - 1st principal component over 48 brain regions

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# Methods: Observational study

- **Covariates:**
  - Model 1:
    - Demographics: age, sex, genetic ancestry
  - Model 2:
    - + Cardiovascular risk factors:
      - BMI, smoking, Hypertension, Diabetes, Hypercholesterolemia
    - + Comorbidities:
      - History of myocardial infarction, atrial fibrillation

- **Statistics:**
  - Multivariable linear regression

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# Methods: Genetic study

- **Design:** two-sample Mendelian Randomization

- **Instrument selection:**
  - P-value < $5x10^{-8}$ / $R^2$ = 0.1 / Minor allele frequency: 0.01 / Palindromic exclusion

- **Exposure:** genetically-determined poor oral health
  - *Gene-Lifestyle Interactions in Dental Endpoints* (GLIDE) *Consortium*
  - 116 genetic variants associated with a composite of caries, dentures and missing teeth



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# Methods: Genetic study

- **Outcome:** Neuroimaging markers
  1. White Matter Hyperintensities (WMH) volume: log-transformation
  2. Fractional Anisotropy (FA):
     - 1st principal component over 48 brain regions
     - Each region individually
  3. Mean Diffusivity (MD):
     - 1st principal component over 48 brain regions
     - Each region individually
  - The estimates for the 116 genetic variants were calibrated for each of the 3 brain health outcomes

- **Statistics:**
  - Inverse-variance weighted MR
  - MR-PRESSO with outlier detection and removal



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# Results: Cohort

| | Total population N = 40,175 | Poor oral health NO N = 34,705 | Poor oral health YES N = 5,470 | P-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Mean age (SD) | 54.96 (7.5) | 54.30 (7.5) | 59.17 (6.6) | <0.001 |
| Female sex (%) | 21,323 (53.1%) | 18,769 (54.1%) | 2,554 (46.7%) | <0.001 |
| **Vascular risk factors** | | | | |
| Hypertension | 7,497 (18.7%) | 6,021 (17.3%) | 1,476 (27.0%) | <0.001 |
| Hypercholesterolemia | 3,419 (8.5%) | 2,709 (7.8%) | 710 (13.0%) | <0.001 |
| Type II diabetes | 1,040 (2.6%) | 810 (2.3%) | 230 (4.2%) | <0.001 |
| Previous smoking | 13,137 (32.8%) | 10,730 (31.0%) | 2,407 (44.1%) | <0.001 |
| Current smoking | 2,467 (6.2%) | 1,917 (5.5%) | 550 (10.1%) | |
| BMI >=25 | 17,159 (42.8%) | 14,664 (42.3%) | 2,495 (45.7%) | <0.001 |
| BMI >=30 | 7,012 (17.5%) | 5,766 (16.6%) | 1,246 (22.8%) | |
| **Comorbidities** | | | | |
| History of atrial fibrillation | 835 (2.1%) | 668 (1.9%) | 167 (3.1%) | <0.001 |
| History of myocardial infarction | 753 (1.9%) | 564 (1.6%) | 189 (3.5%) | <0.001 |

# Results: Observational study

Table. Linear regression results: neuroimaging brain health traits as a function of oral health status.

| Outcome | White matter hyperintensity volume | | Fractional Anisotropy | | Mean Diffusivity | |
|---|---|---|---|---|---|---|
| | Beta (SE) | P | Beta (SE) | P | Beta (SE) | P |
| Univariate | 0.46 (0.016) | <0.001 | 0.41 (0.016) | <0.001 | 0.42 (0.016) | <0.001 |
| Multivariate Model 1 | 0.12 (0.014) | <0.001 | 0.13 (0.013) | <0.001 | 0.07 (0.013) | <0.001 |
| Multivariate Model 2 | 0.09 (0.014) | <0.001 | 0.10 (0.013) | <0.001 | 0.05 (0.013) | <0.001 |

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# Results: Genetic study

Table. Mendelian Randomization results. Outcomes are association tests against aggregate metrics for FA/MD in UKB.

| Outcome | Primary Mendelian Randomization Analysis | | | Corrected Mendelian Randomization Analysis | | |
|---|---|---|---|---|---|---|
| | Number of instruments | Beta (SE) | P value | Number of instruments | Beta (SE) | P value |
| White matter hyperintensity volume | 116 | 0.30 (0.06) | <0.001 | 109 | 0.37 (0.06) | <0.001 |
| Fractional anisotropy | 116 | 0.43 (0.06) | <0.001 | 111 | 0.45 (0.06) | <0.001 |
| Mean diffusivity | 116 | 0.10 (0.03) | 0.004 | 114 | 0.08 (0.03) | 0.009 |

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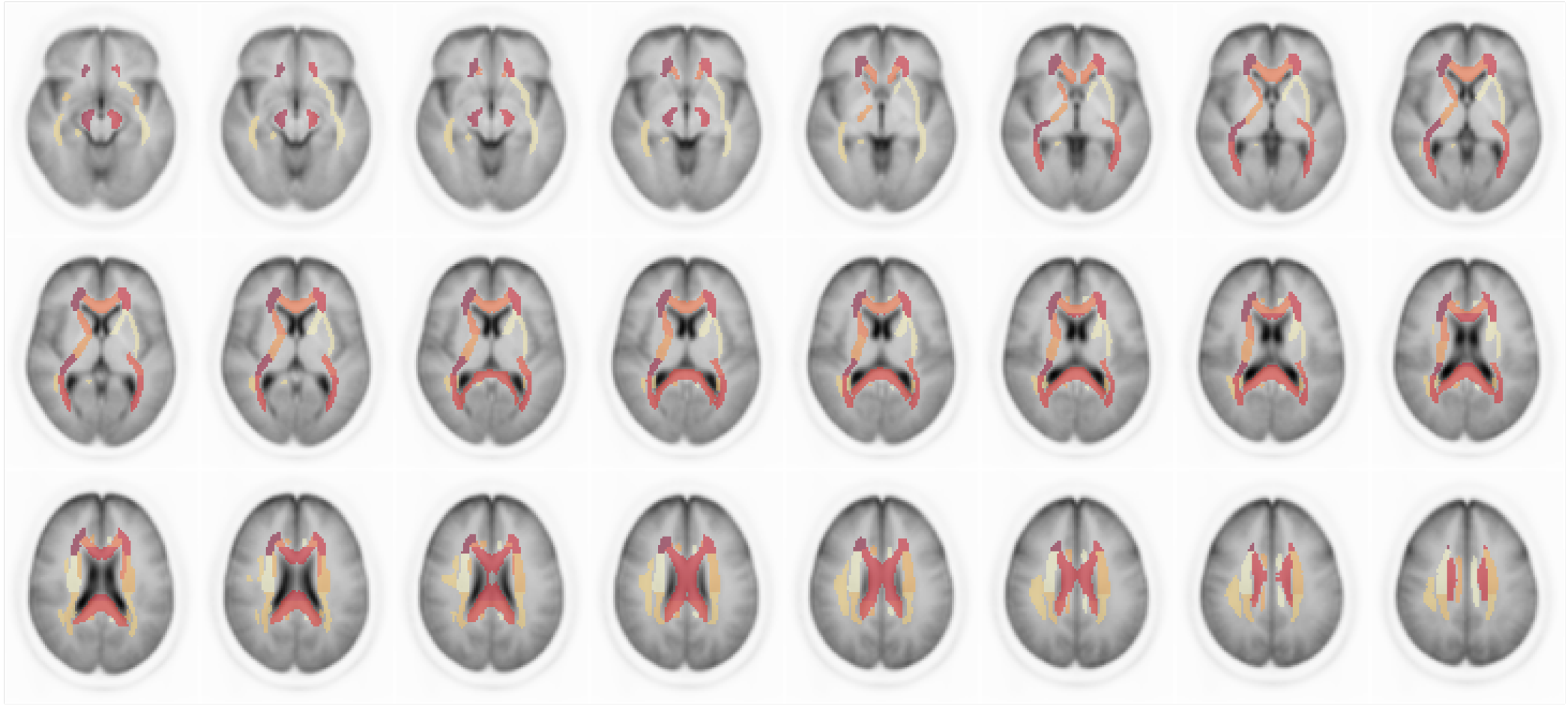
# Results : Area-specific results for Fractional Anisotropy




*Rivier et al. Neurology 2023. In press*

# Conclusion

- Among persons without stroke, genetically-determined poor oral health is associated with worse neuroimaging brain health profiles.
    - Because gene-disease associations are less prone to confounding, these results provide evidence that this association is causal.

- Oral health is relatively easy and inexpensive to improve upon.

- The neuroimaging markers evaluated precede the onset of stroke and dementia by many years, suggesting that oral health may be a promising target for interventions focused on improving brain health.

# POLL QUESTION 3

# Pathophysiological hypotheses

1. Neuroinflammation via systemic inflammation
    1. Poor oral health leads to an increase systemic proinflammatory mediators
    2. Systemic inflammation contributes to neuroinflammation (due to the interdependence of peripheral and central immune systems)
    3. Especially when chronic, neuroinflammation leads to:
        1. Activation of microglia and complement system
        2. Neurodegeneration, neuronal death and lowered neurogenesis
        3. Altered white matter integrity (evidenced by changes in Fractional Anisotropy and Mean Diffusivity)
        4. Lower gray and white matter volumes
        5. Cognitive deterioration, including decreased global cognition and executive functioning

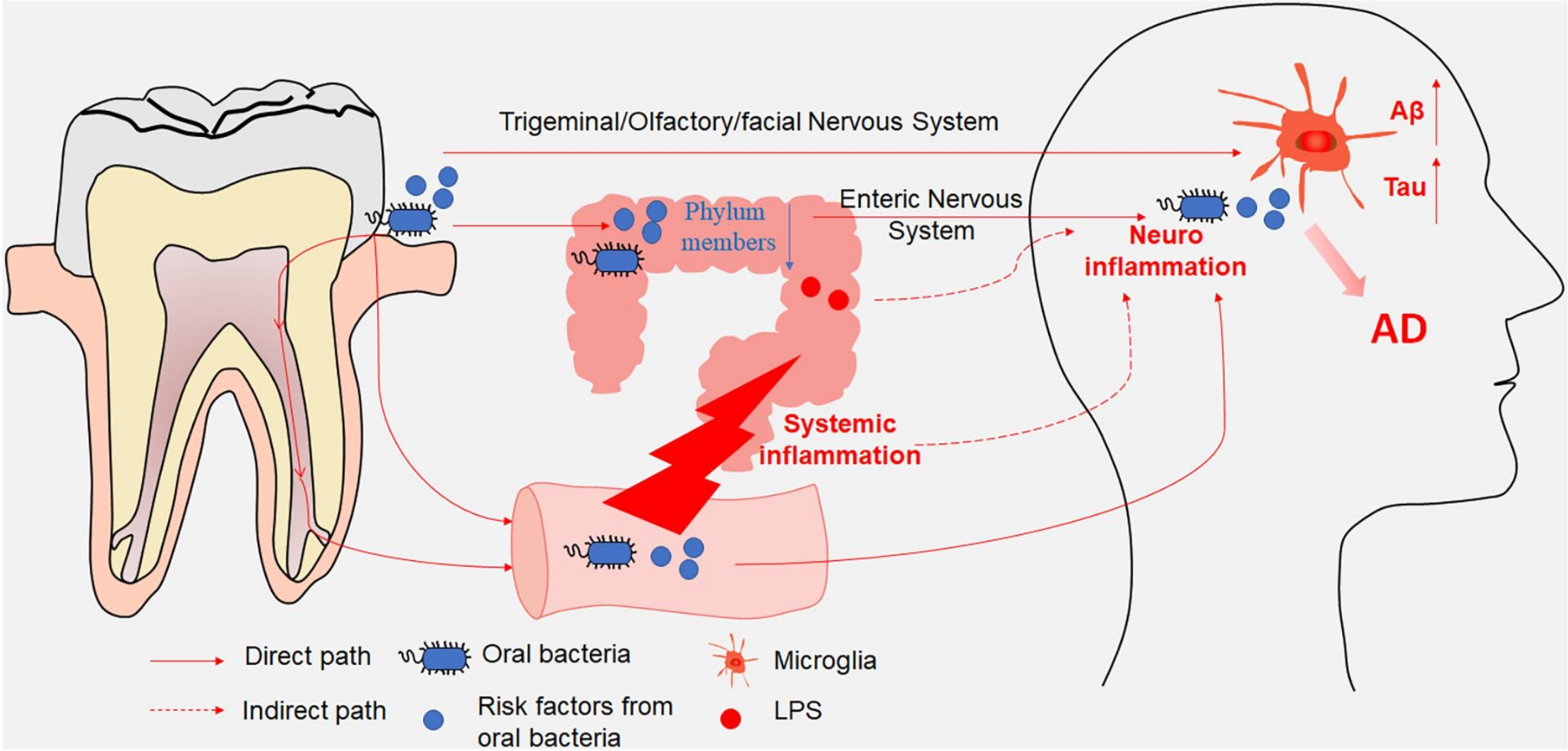
*J Am Geriatr Soc 2022 Sep;70(9):2695-2709*

# Pathophysiological hypotheses

2. Oral-Gut-Brain axis
    1. The oral microbiota is the second-largest microbiota in the human body following the gut one
    2. Microbial biofilm maintains a homeostatic balance with the host, but can become dysbiotic, indicating a shift in bacteria species.
    3. Direct effect: oral microbes can spread through cranial nerves (trigeminal) and cause CNS damage.
    4. Indirect effect: transmission through the bloodstream
        1. Bacteria and bacterial products can enter the systemic circulation from the periodontal cavity.
        2. Pathogens developing on dentures biofilm are found in atherosclerotic plaques.
        3. Oral microbes and their toxic metabolites may damage the blood-brain barrier (permeability increases with age)
    5. Once in the brain, bacterial products can :
        1. Aggravate neuroinflammation
        2. Trigger amyloid deposition and Tau protein phosphorylation

*Front Cell Neurosci 2021 Apr 14:15:633735.*

# The Oral-Gut-Brain axis




*Front Cell Neurosci 2021 Apr 14:15:633735.*

# Pathophysiological hypotheses

3. Tooth loss may impair cognition by reducing sensorimotor stimulation from the masticatory apparatus.
    1. Loss of occlusal support can change brain's blood supply and affect cognitive ability
        1. May lead to atrophic brain changes
    2. Mastication (chewing) increases blood flow in the temporal region

4. Tooth loss and masticatory pain may lead to changes in dietary intake and diversity
    1. Dietary changes can result int nutritional deficiencies
    2. Nutritional deficiencies are risk factors for cognitive impairment and dementia (vitamins mostly)



*J Dent Resactions. 2007 Jan;86(1):64-8.*
*Front Neurosci. 2022; 16: 811335.*

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NEURO CRITICAL CARE SOCIETY


Thank you!


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# Question 1

What is known regarding the link between oral health and brain health?
(Multiple choices possible)

a) Poor oral health is associated with cognitive decline.

b) Cavities cause glioblastoma (a type of brain tumor).

c) Stress is a risk factor for both periodontitis and stroke.

d) Poor cognitive function is associated with poor oral health.

# Question 2

Why is Mendelian Randomization considered a useful tool for causal inference? (1 correct choice)

a) It relies on randomized controlled trials.

b) It uses genetic variants randomly assorted at conception.

c) It uses observational data only.

d) It is based on theoretical assumptions.

# Question 3

What could be the factors mediating the link between oral health and brain health?

(Multiple choices possible)

a) Systemic inflammation

b) Bacterias and bacterial toxins reaching the bloodstream

c) Changes in dietary intake due to tooth loss

d) Oral microbes spreading through cranial nerves