Poor oral health increases heart disease: Evidence from Mendelian randomization using genomic structural equation modeling

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Background

Inclusion of genetic information in surveys presents opportunities for causal identification of chronic disease pathways.

- Periodontitis is thought to increase risk of heart disease through chronic inflammation, but there is little causal evidence.
- Medicare expenditures to treat heart disease exceed $55 billion.
- Determining the cost offset of lower treatment costs from improved oral health is critical to evaluation of a Medicare Part B dental benefit.

We use variation in the genetic determinants of poor oral health (periodontitis, dental caries, lost teeth) to estimate the effect of edentulism (loss of all permanent teeth) on heart disease measures.

Genetic regions affecting susceptibility to periodontitis: FcgRIIala, interleukin (IL)-1a, IL-1b, IL-6, IL-8, IL-10, IL-37, matrix metalloproteinase 2 (MMP2), MMP3, MMP8, MMP9 and VDR

Health and Retirement Survey

- Nationally representative of U.S. population age > 50.
- Includes socio-demographics, health insurance, schooling, parent's education
- Genotyping during 2006-2020.
- N = 17, 127 people observed ~ 7.7 years
- Heart disease measures: heart problem, CVD, stroke, heart attack, angina, CHF.

Construct **polygenic score** (PGS) to serve as an instrumental variable that identifies effect of edentulism on heart disease.

Estimation of SEM

Use GWAS-by-subtraction structural equation model (SEM) to estimating factor loadings.

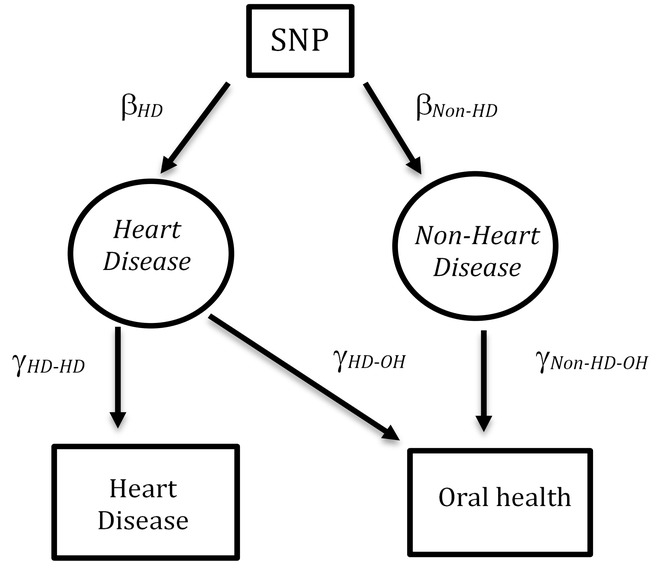
$$PGS_i = \sum_{j=1}^{J} \hat{\gamma}_{Non-HD-OH,j} G_{ij},$$

$j = 1, \ldots, J$ indexes SNPs and $G_{ij} \in \{0,1,2\}$ is the number of effect alleles at SNP j.

$$CVD\ outcome_{it} = \alpha_1 + \beta_1 \cdot Edentulous_{it} + \boldsymbol{\gamma_1'} \boldsymbol{X_{it}} + \omega_{1t} + \varepsilon_{1it},$$

$$Edentulous_{it} = \alpha_2 + \beta_2 \cdot \widetilde{PGS}_i + \boldsymbol{\gamma_2'} \boldsymbol{X_{it}} + \omega_{2t} + \varepsilon_{2it},$$

$\boldsymbol{X_{it}}$ is a vector of control variable for person i in year t, ω_{1t} and ω_{2t} are wave fixed effects and $\widetilde{PGS}_i$ is the normalized PGS instrument.



- SNP / GWAS data: ▭
- Latent factors: ◯
- Linear associations: $Y \longrightarrow X$

Results

We calculate different PGS based on p-value cutoffs & for different ancestral groups (European, African, Hispanic).

Outcome measure	OLS	PGS IV (p < 0.001)	PGS IV (p ≤ 1)
Heart problem, past 2 yrs.	0.006**	0.054	0.034
Dr. ever told of heart problem	0.069***	0.483***	0.488***
CVD since 1st wave	0.025**	0.273	0.327***
CVD/stroke since 1st wave	0.035***	0.482	0.377***
Heart attack, past 2 yrs.	0.007***	0.069***	0.039***
Angina, past 2 yrs.	0.012***	0.118	0.076
Cong. heart failure, past 2 yrs.	0.016***	0.121	0.067

Edentulism increases the likelihood of ever being told of heart disease & heart attack in past two years.

- 48 pp increase in past heart disease.
- 3.9 – 6.9 pp increase in heart attack.

Conventional PGS IVs over-estimate treatment effects by 23% – 41%.

Failing to account for cost offsets will over-estimate cost of Medicare Part B dental benefit.

Falsification test: Model predicts no effect of poor oral health on cancer, psychiatric problems and sleep disorders

Balance test: Controls are similar for high and low values of instrument

Acknowledgement / Disclaimer / COI

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