

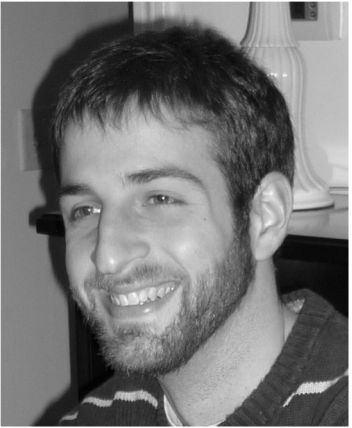


Genomic risk through the lifespan

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Acknowledgements



Mark Chaffin



**Sekar
Kathiresan**

Institutional Support



BROAD
INSTITUTE

Funding



National Human Genome
Research Institute

Clinical observation

Family history of heart attack linked to increased risk

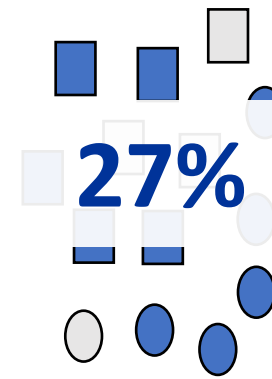


YOUNG CANDIDATES FOR CORONARY HEART DISEASE

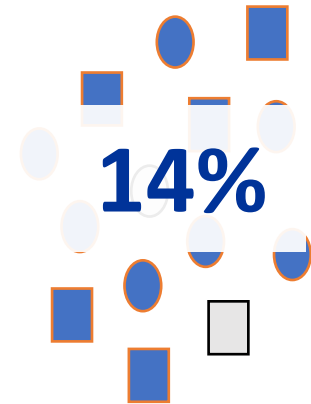
*Menard M. Gertler, M.D., New York, Stanley M. Garn, Ph.D.,
and
Paul D. White, M.D., Boston*

JAMA (1951)

Family
History



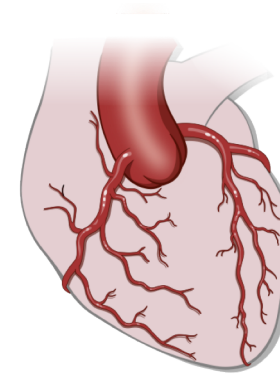
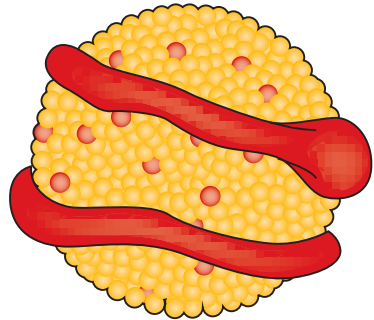
Cases
N = 100



Controls
N = 146

Traditional approach to DNA-based prediction focused on rare, **monogenic** mutations

Familial hypercholesterolemia



↑ Cholesterol

Heart attack
3x increased risk

0.4% of the population

How might DNA predispose to heart attack?

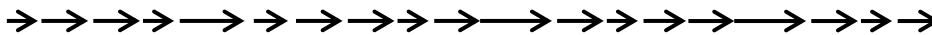
2 models – monogenic and polygenic

Monogenic

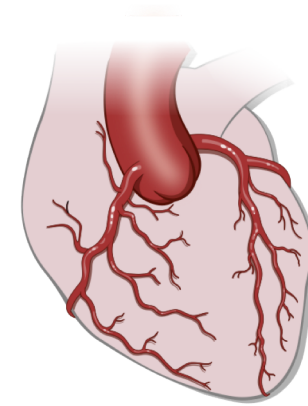


Rare driver mutation in each individual

Polygenic



Cumulative impact of many variants



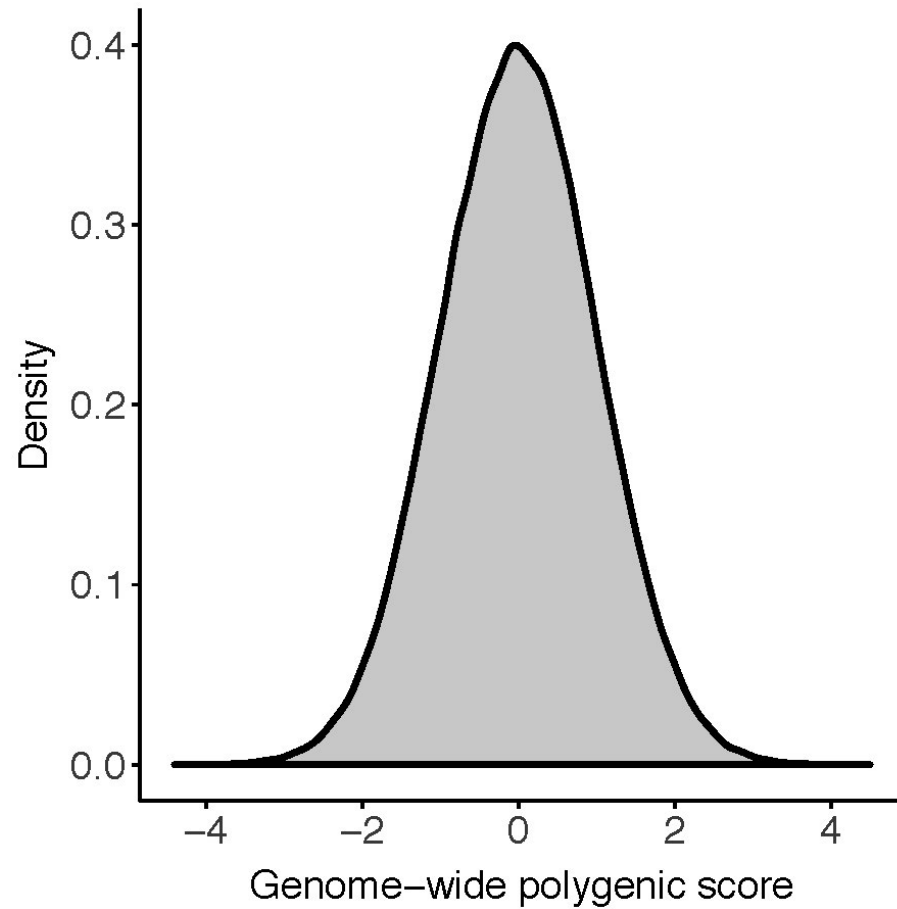
Can a polygenic score identify individuals with risk equivalent to a monogenic mutation?

Khera,* Chaffin,* ... Kathiresan | *Nat Genetics* | 2018

Khera,* Chaffin,* ... Kathiresan | *Circulation* | 2018

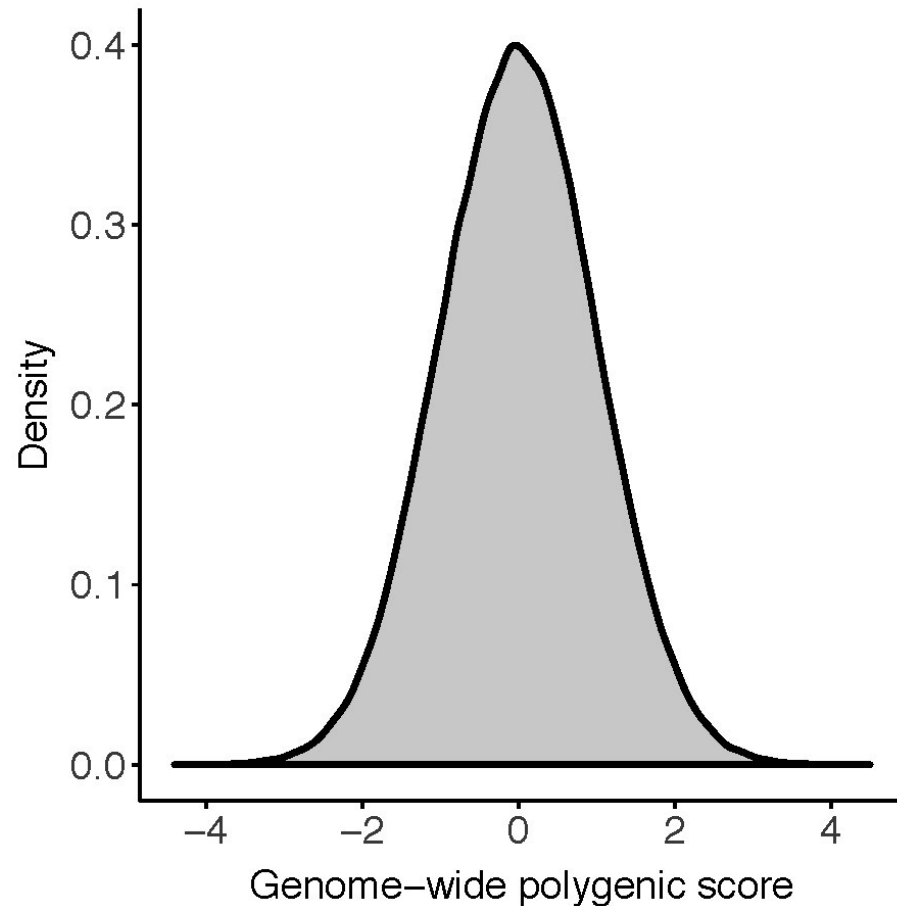
Test genome-wide polygenic score in 300,000 additional people

**Normally distributed in
population**

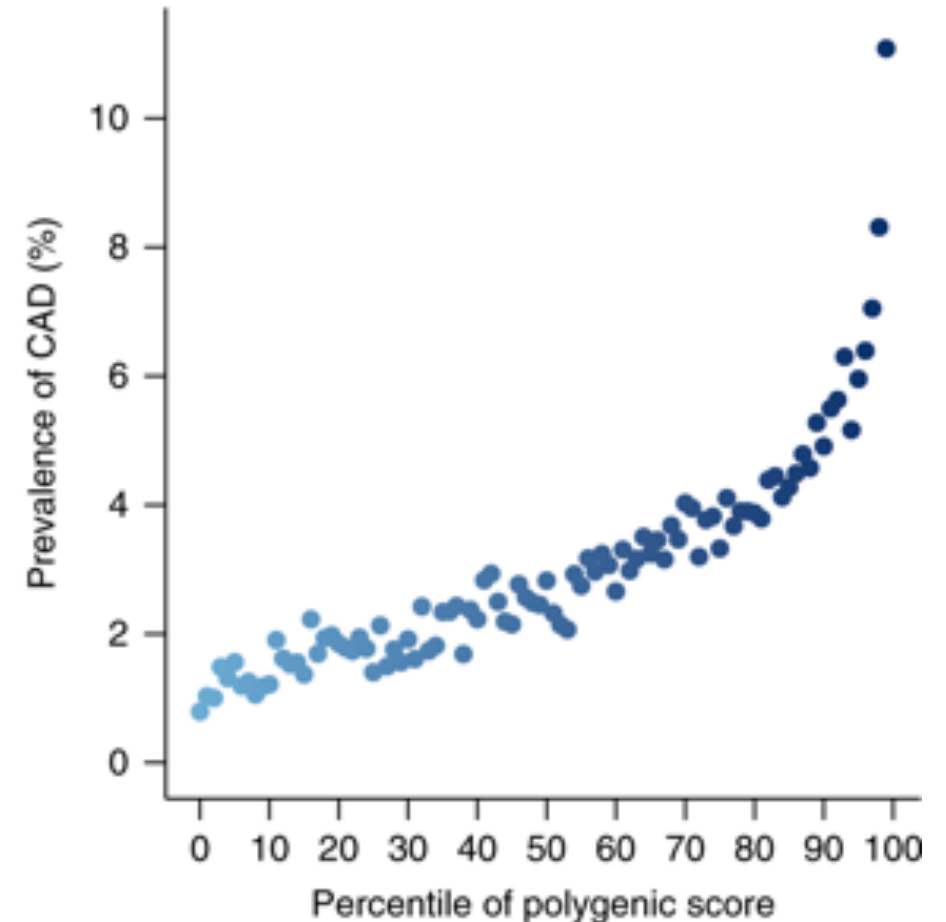


Test genome-wide polygenic score in 300,000 additional people

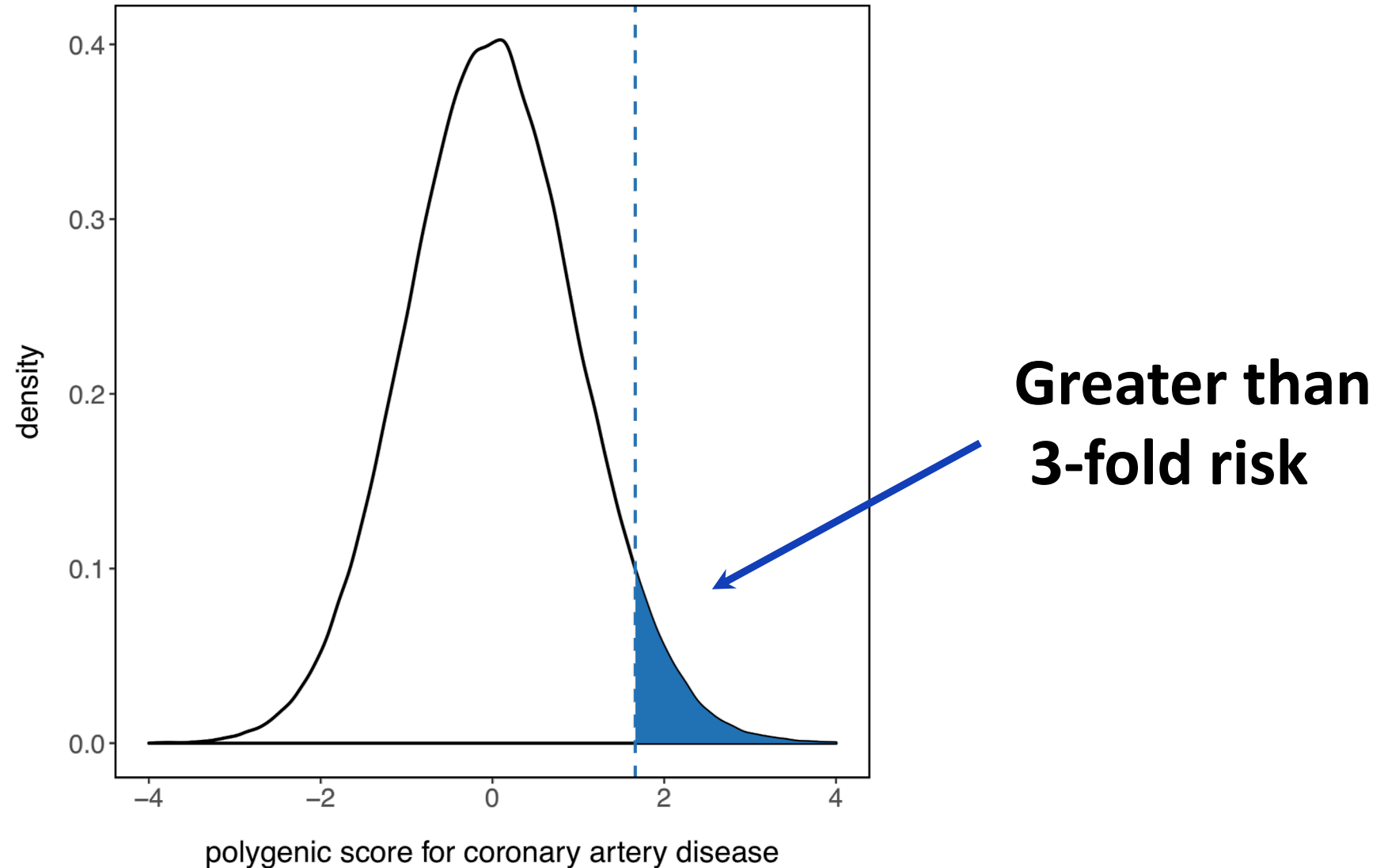
**Normally distributed in
population**



**Significant gradient
in risk**



Top 8% of the population has polygenic risk equivalent to a monogenic mutation



Traditional risk factors used in clinical practice are inadequate to pinpoint at-risk patients

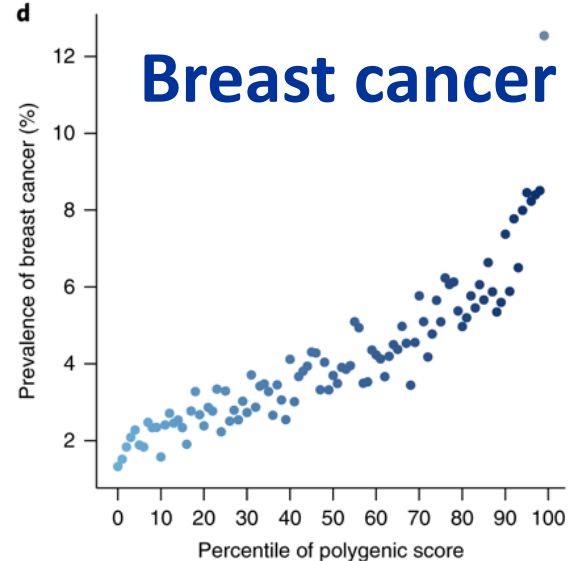
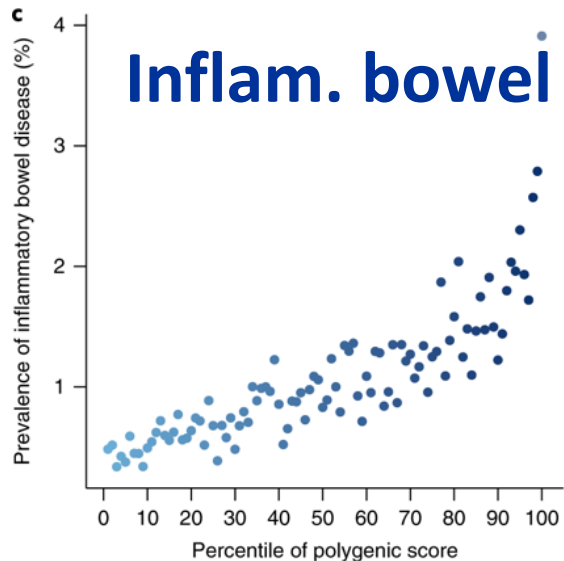
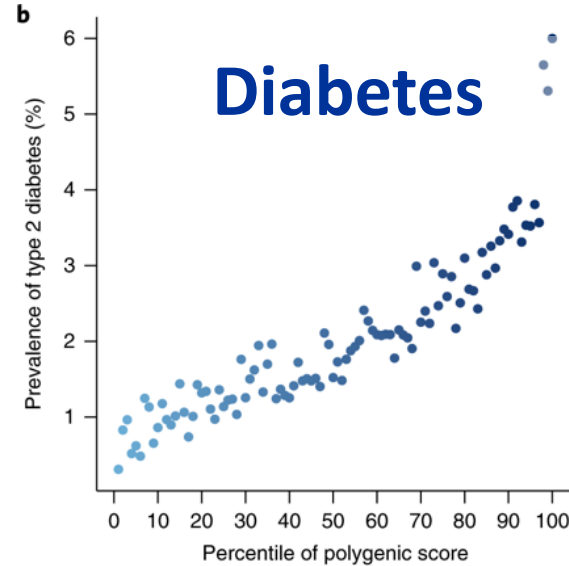
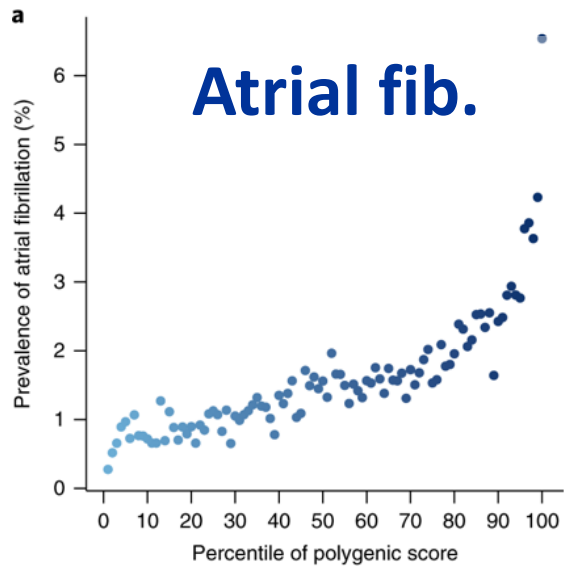
	Remainder of population	Top 8% of polygenic score
Family history	35%	44%
Hypertension	28%	32%
Type 2 diabetes	2%	2.7%
Hypercholesterolemia	13%	20%
Current smoking	9.2%	9.5%
Body mass index	27.3	27.7
Systolic blood pressure	140	141

***Some traditional risk factors are slightly elevated,
but not enough to be useful***

Genome-wide polygenic score for heart attack identifies **20x** than monogenic mutations

	Monogenic	Polygenic
Prevalence	0.4%	8%
Odd ratio for MI	3x	3x
Mode of detection	↑ LDL-cholesterol	Currently undiagnosed
Intervention	Statin, ezetimibe PCSK9i	Lifestyle Medication

Approach works for **other common diseases** . . . including those without monogenic risk factors



**% of population
at >3-fold risk**

Heart attack **8.0%**

Atrial fibrillation **6.1%**

Diabetes **3.5%**

Inflam. bowel **3.2%**

Breast cancer **1.5%**

How does polygenic susceptibility to obesity impact weight over the lifespan?

Khera,* Chaffin,* ... Kathiresan | *Cell* | 2019

Genome-wide polygenic score for obesity

2.1 million variants

Discovery GWAS
2.1 million variants
N > 300,000

ARTICLE

doi:10.1038/nature14177

Genetic studies of body mass index yield new insights for obesity biology

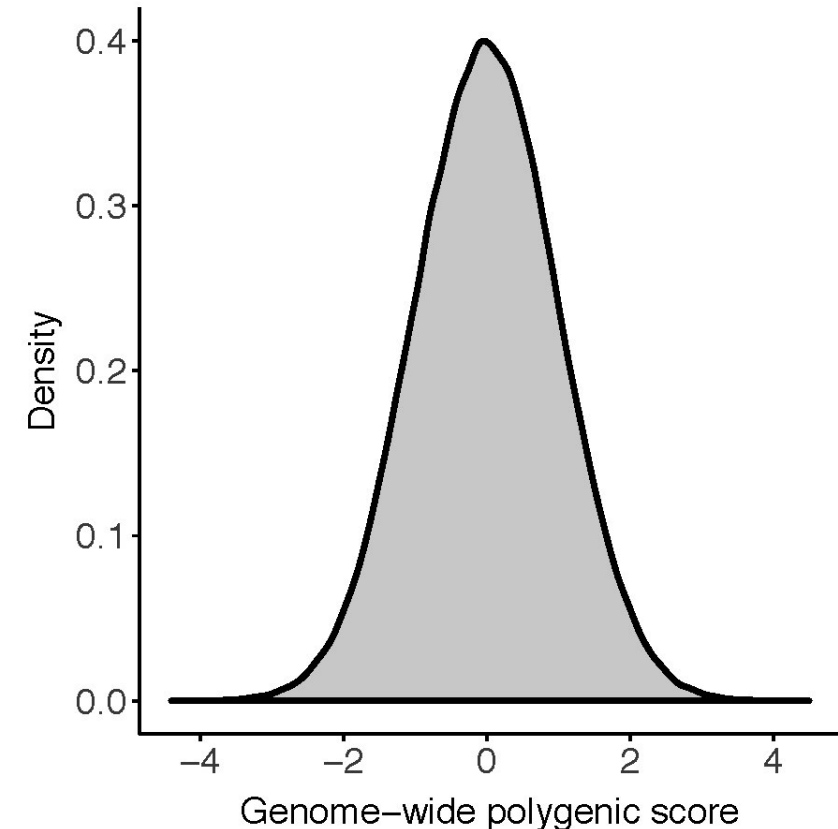
A list of authors and their affiliations appears at the end of the paper

Obesity is heritable and predisposes to many diseases. To understand the genetic basis of obesity better, here we conduct a genome-wide association study and Metabochip meta-analysis of body mass index (BMI), a measure commonly used to define obesity and assess adiposity, in up to 339,224 individuals. This analysis identifies 97 BMI-associated loci ($P < 5 \times 10^{-8}$), 56 of which are novel. Five loci demonstrate clear evidence of several independent association signals, and many loci have significant effects on other metabolic phenotypes. The 97 loci account for ~2.7% of BMI variation, and genome-wide estimates suggest that common variation accounts for >20% of BMI variation. Pathway analyses provide strong support for a role of the central nervous system in obesity susceptibility and implicate new genes and pathways, including those related to synaptic function, glutamate signalling, insulin secretion/action, energy metabolism, lipid biology and adipogenesis.

Locke et al. 2015

Normal distribution

N = 288,016



Impact of polygenic obesity to obesity in Middle age

UK Biobank

288,016 participants

Mean age 57

Impact of polygenic obesity to obesity in Middle age

UK Biobank

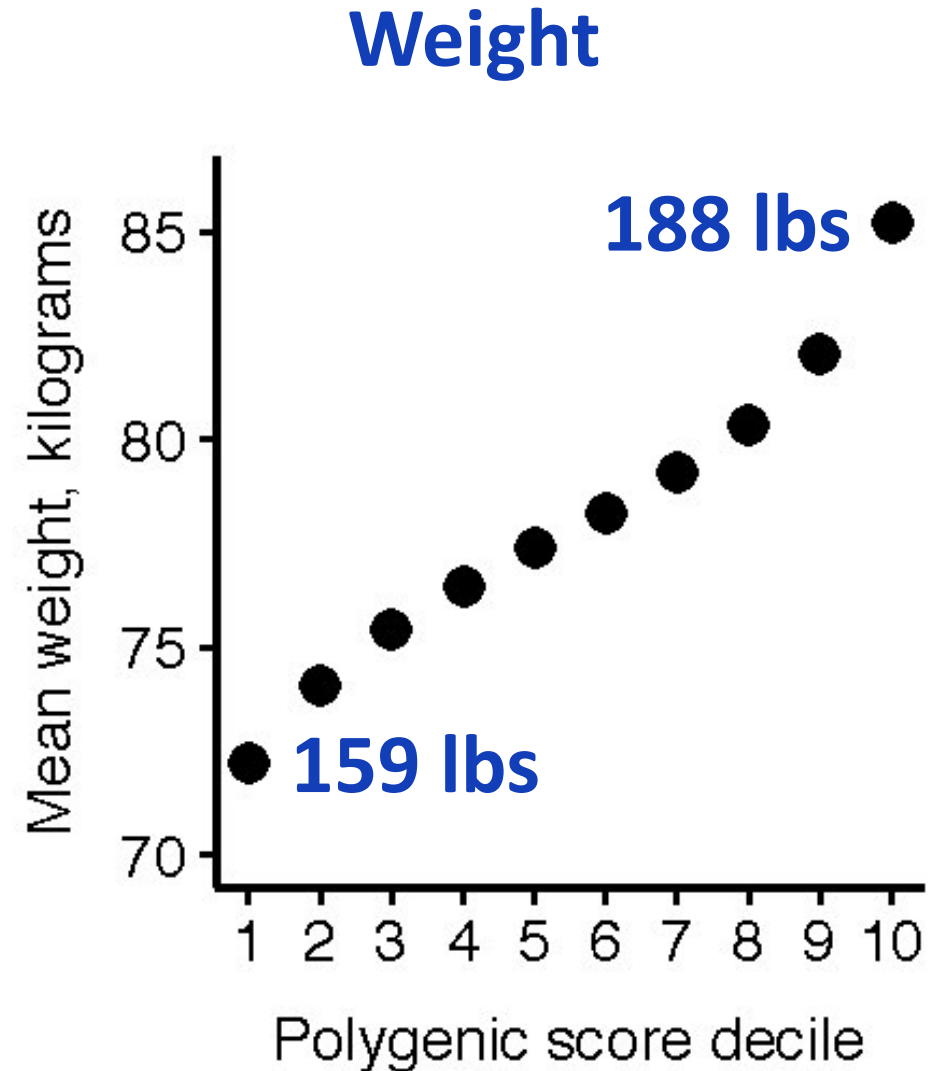
288,016 participants

Mean age 57

Gradient across deciles

29 pounds

+ 4.8 kg/m²



Impact of polygenic obesity to obesity in Middle age

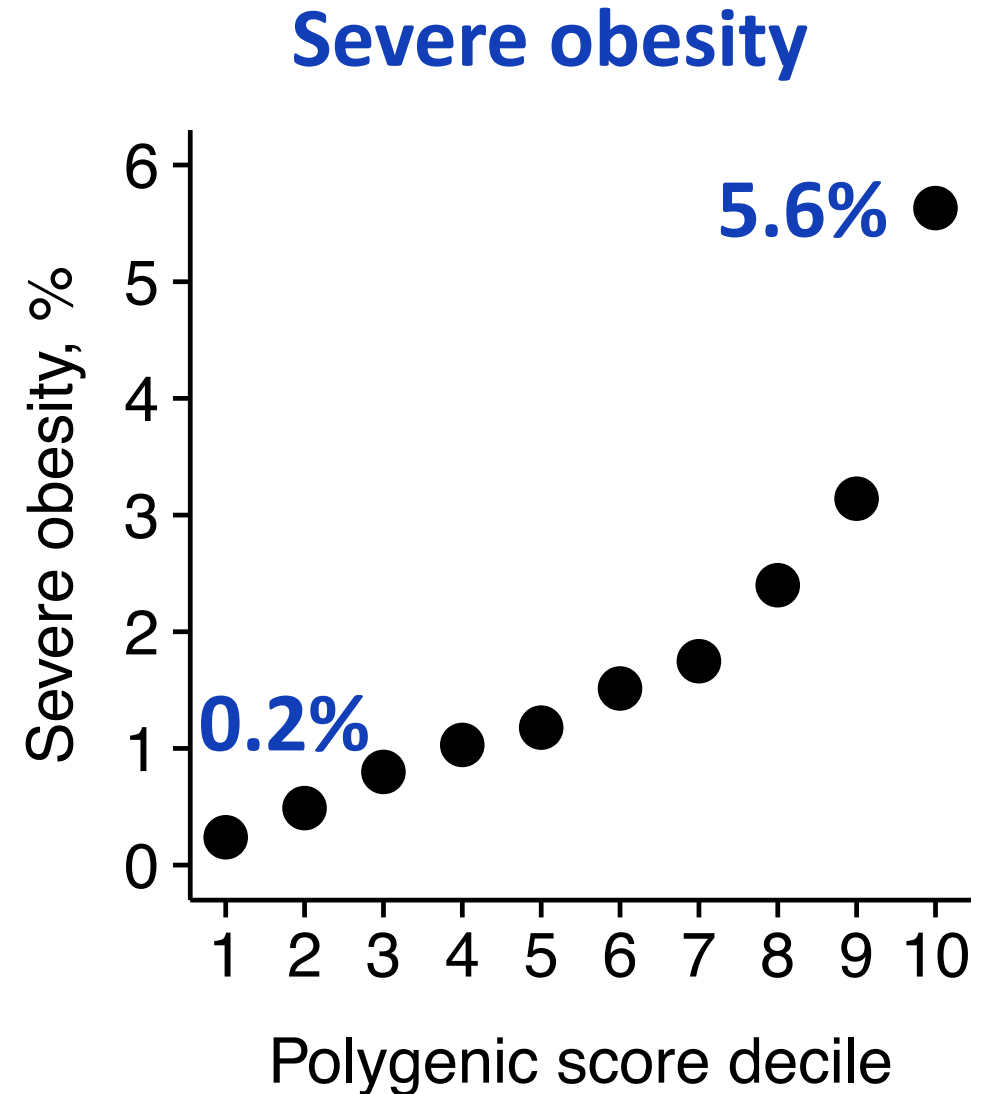
UK Biobank

288,016 participants

Mean age 57

Gradient across deciles

25-fold



Impact of polygenic obesity to obesity in Young adulthood

Framingham / CARDIA

3,722 participants

Mean age 28

Followed 27 years

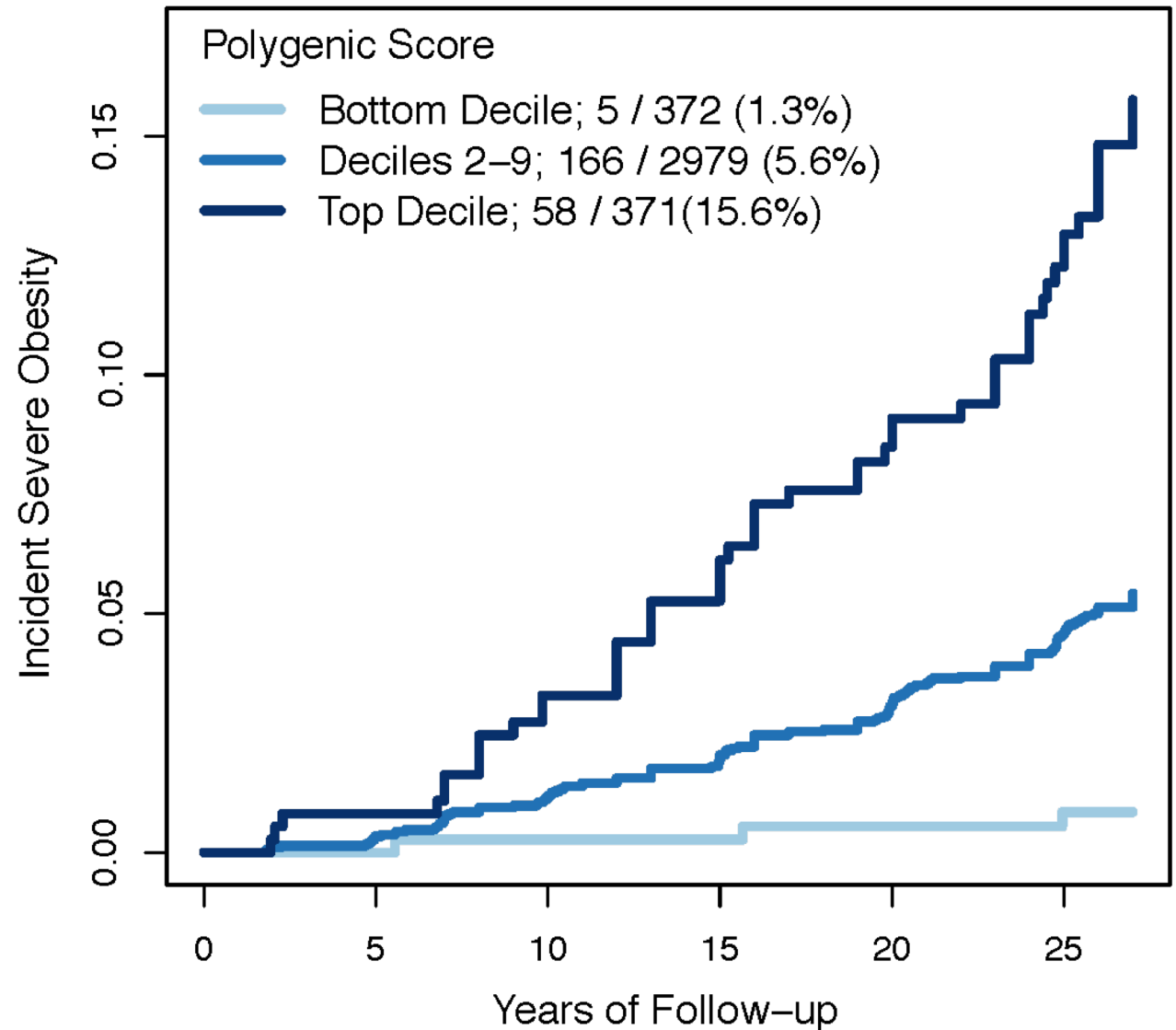
Impact of polygenic obesity to obesity in Young adulthood

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Mean age 28

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Impact of polygenic obesity to obesity in childhood

Birth – 18 years

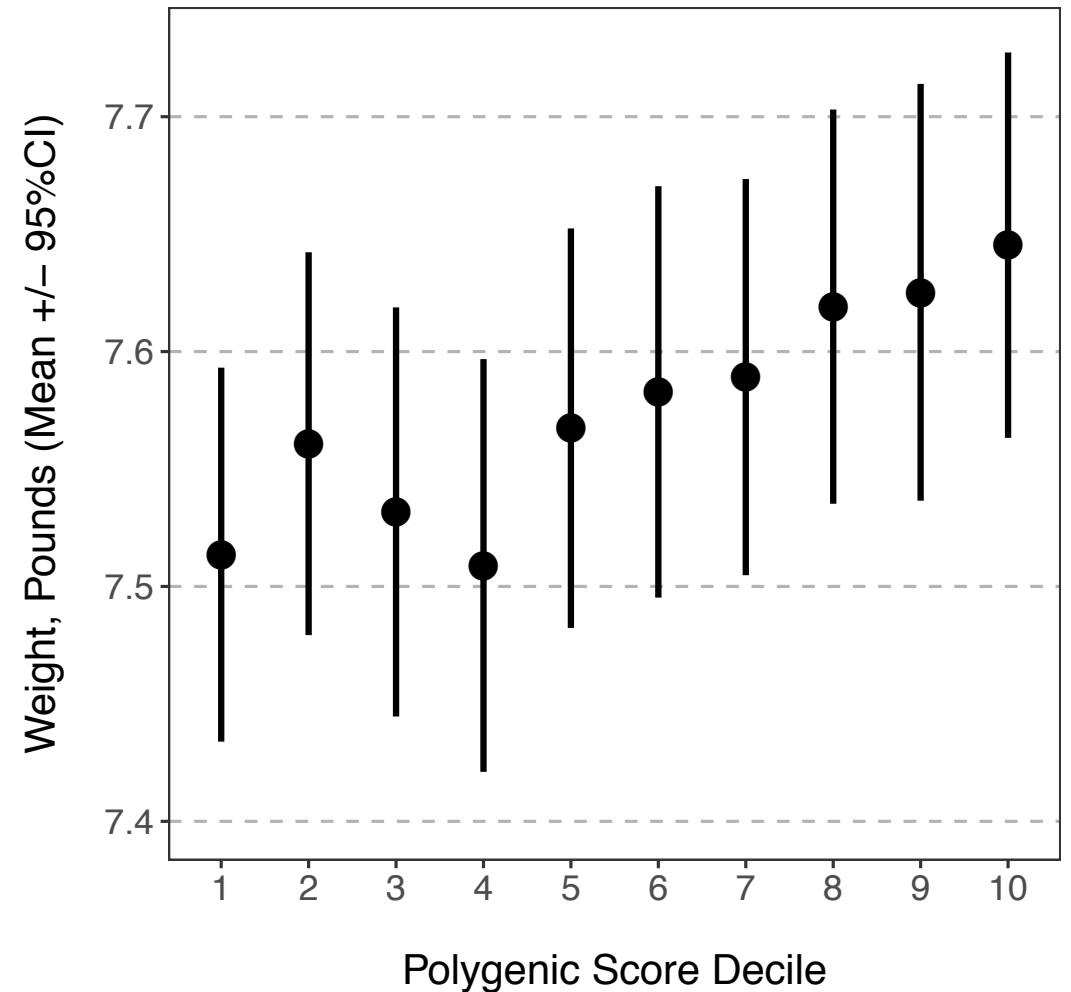
ALSPAC birth cohort

7,425 participants

Recruited 1991-1992

Followed birth to age 18

Birth



Impact of polygenic obesity to obesity in childhood

Birth – 18 years

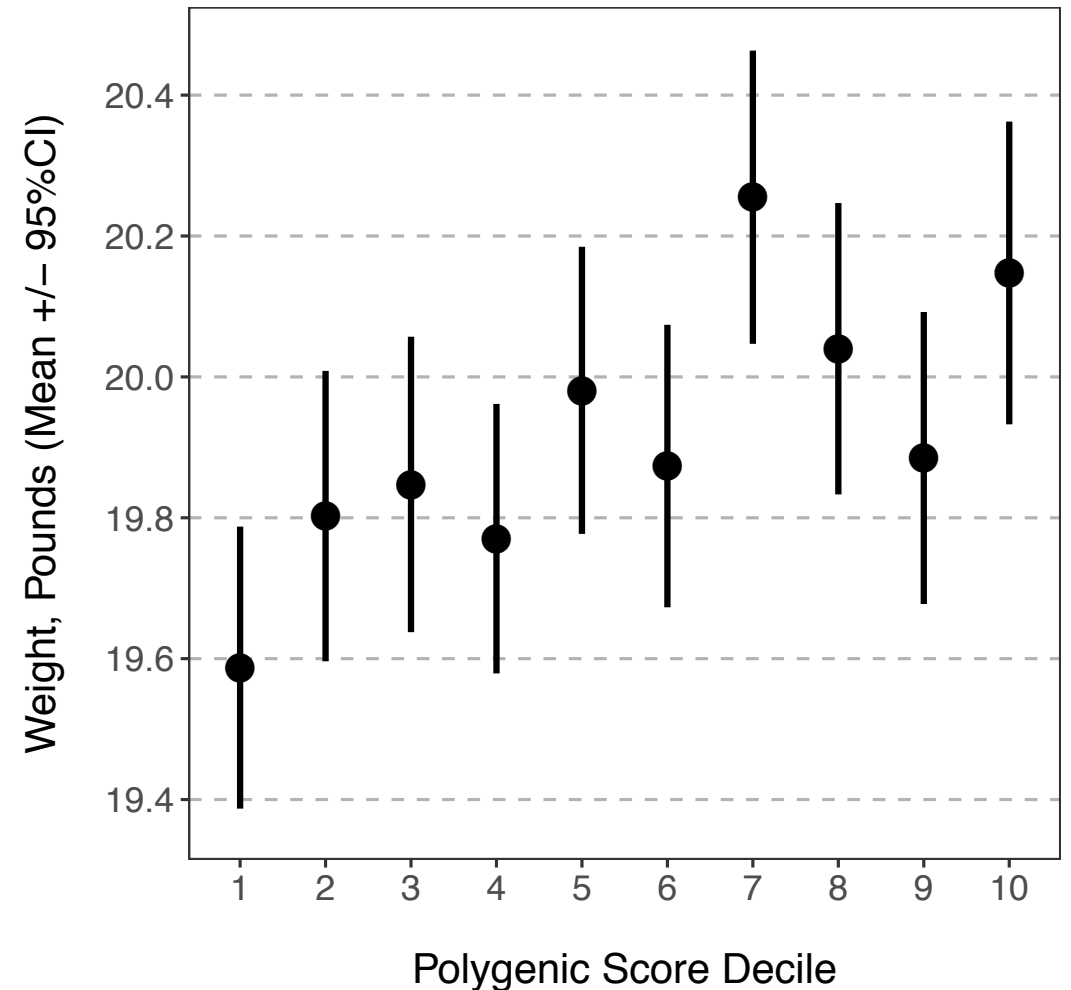
ALSPAC birth cohort

7,425 participants

Recruited 1991-1992

Followed birth to age 18

8 months



Impact of polygenic obesity to obesity in childhood

Birth – 18 years

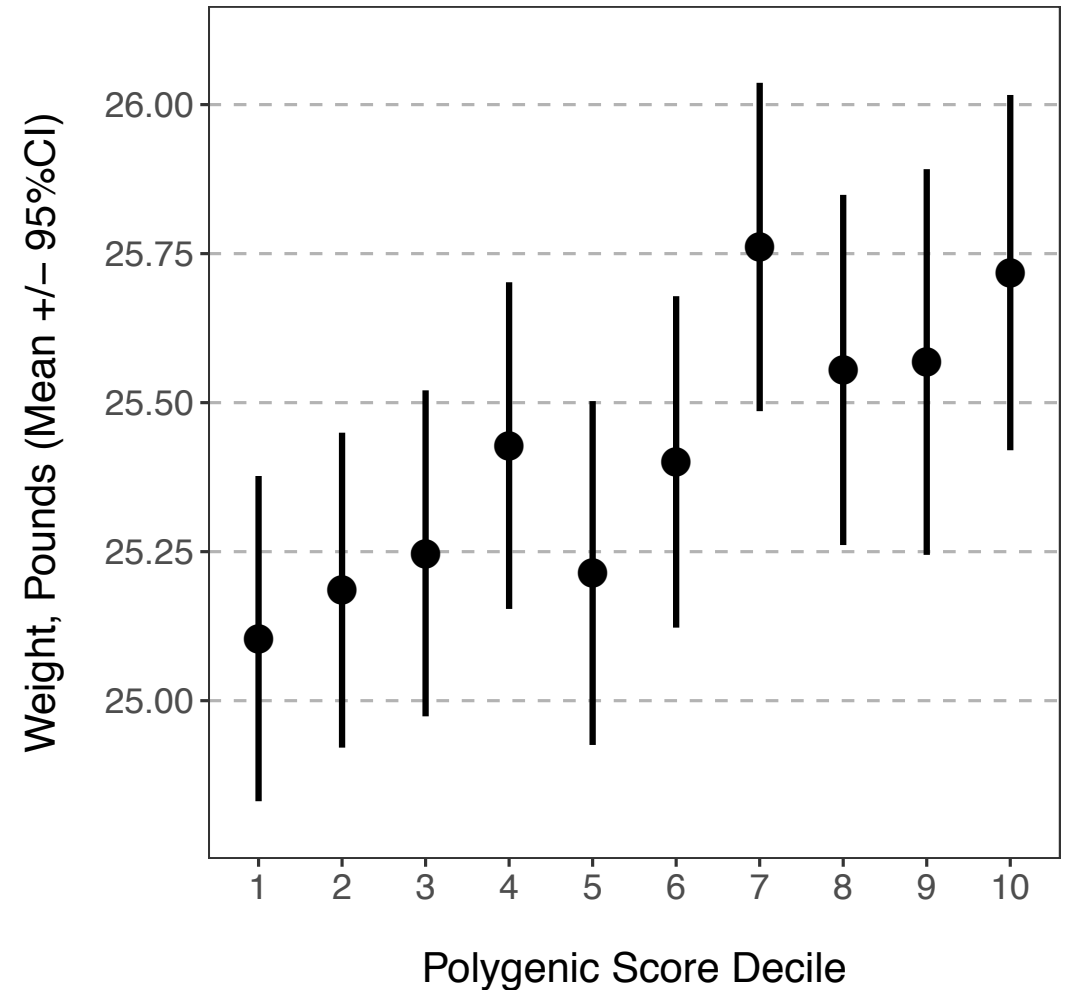
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Impact of polygenic obesity to obesity in childhood

Birth – 18 years

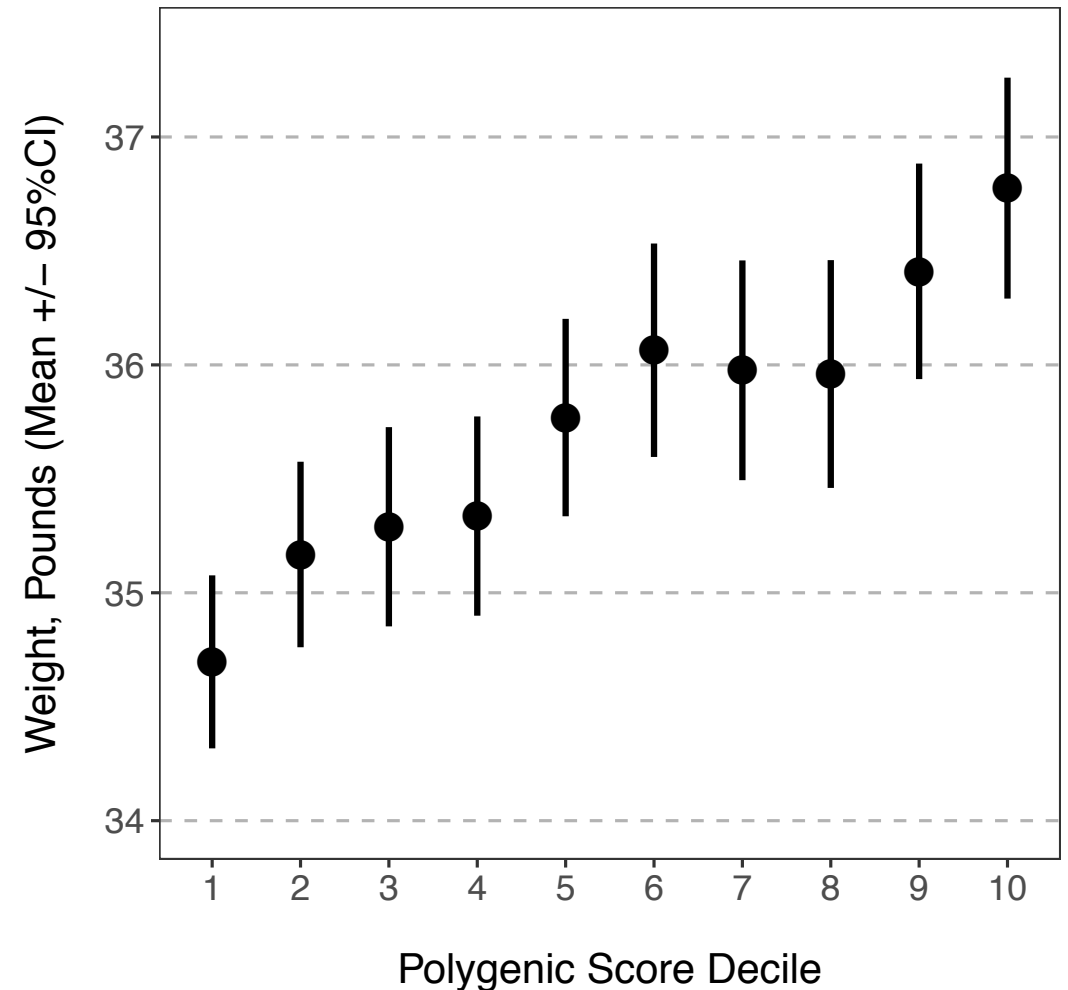
ALSPAC birth cohort

7,425 participants

Recruited 1991-1992

Followed birth to age 18

3.5 years



Impact of polygenic obesity to obesity in childhood

Birth – 18 years

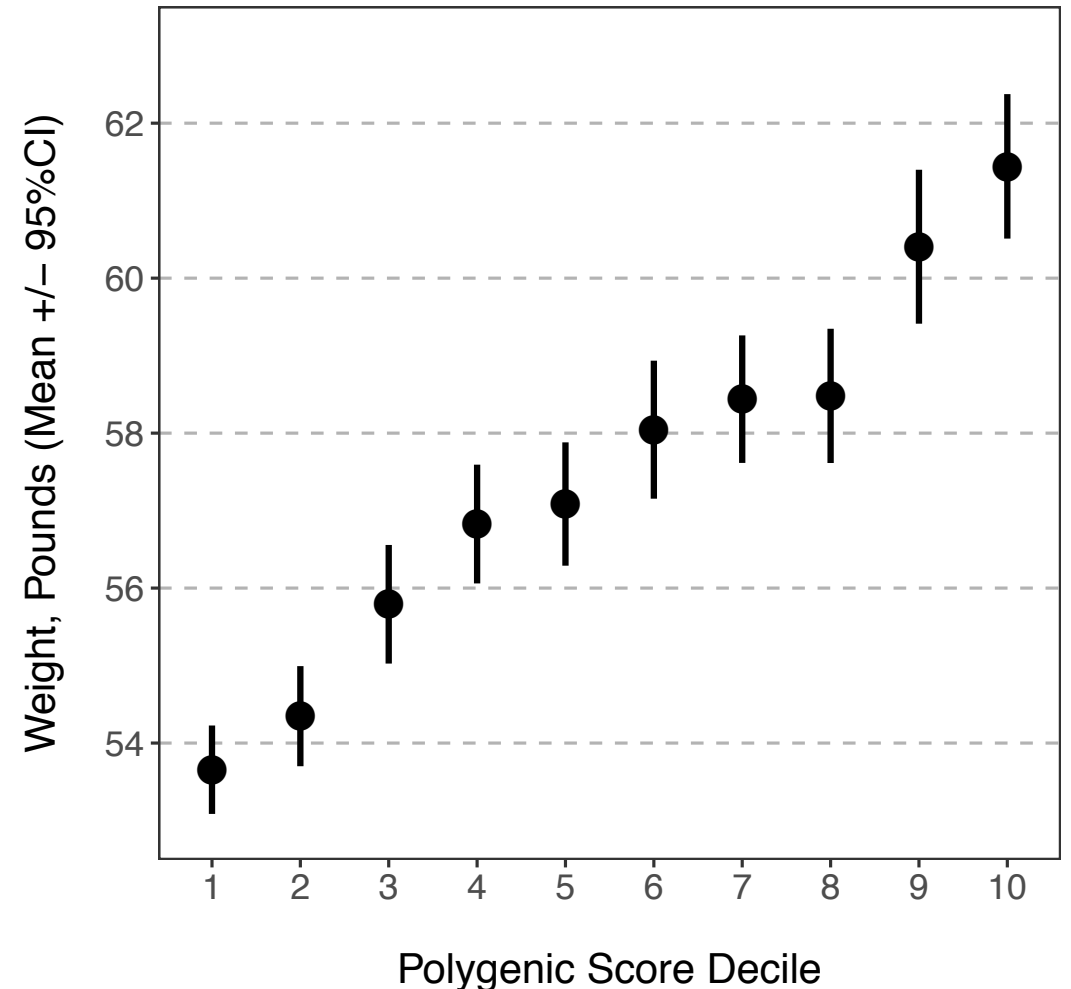
ALSPAC birth cohort

7,425 participants

Recruited 1991-1992

Followed birth to age 18

8 years



Impact of polygenic obesity to obesity in childhood

Birth – 18 years

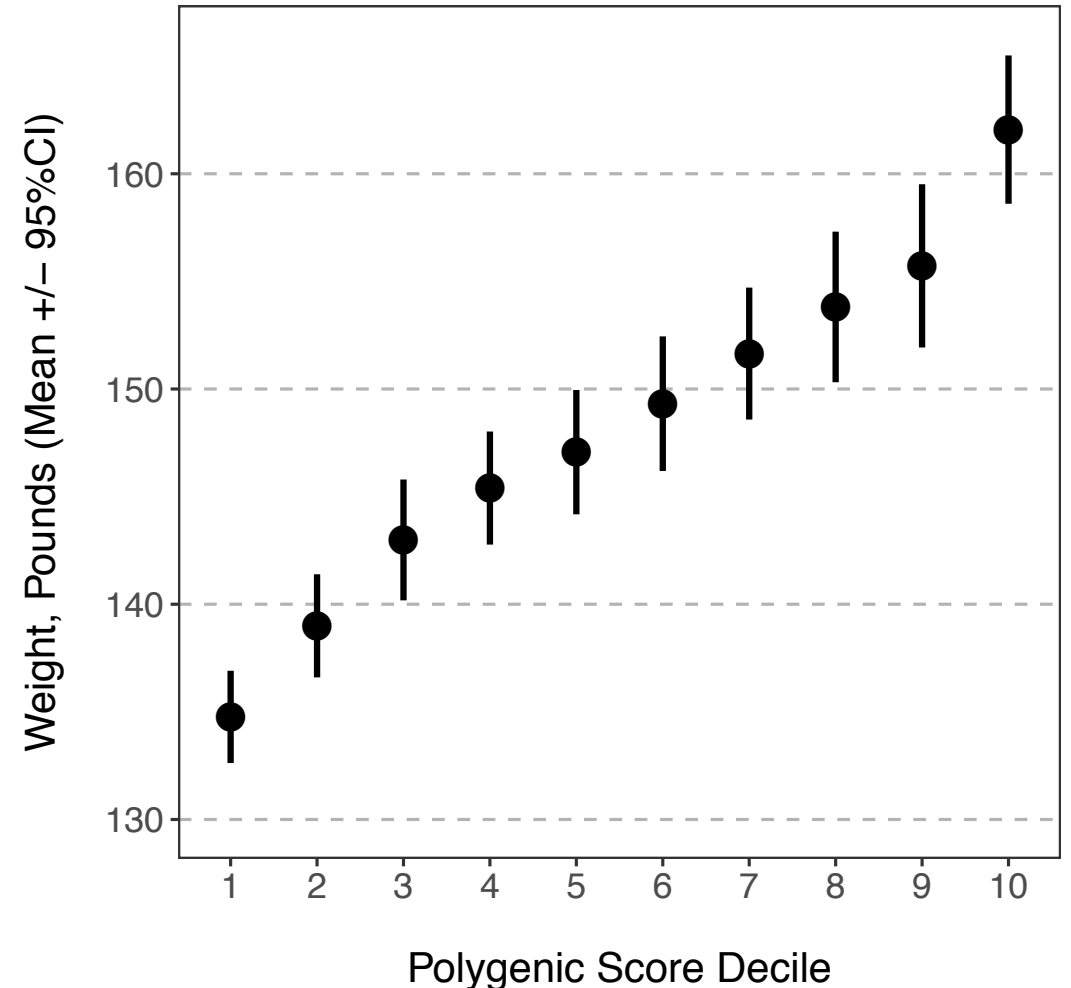
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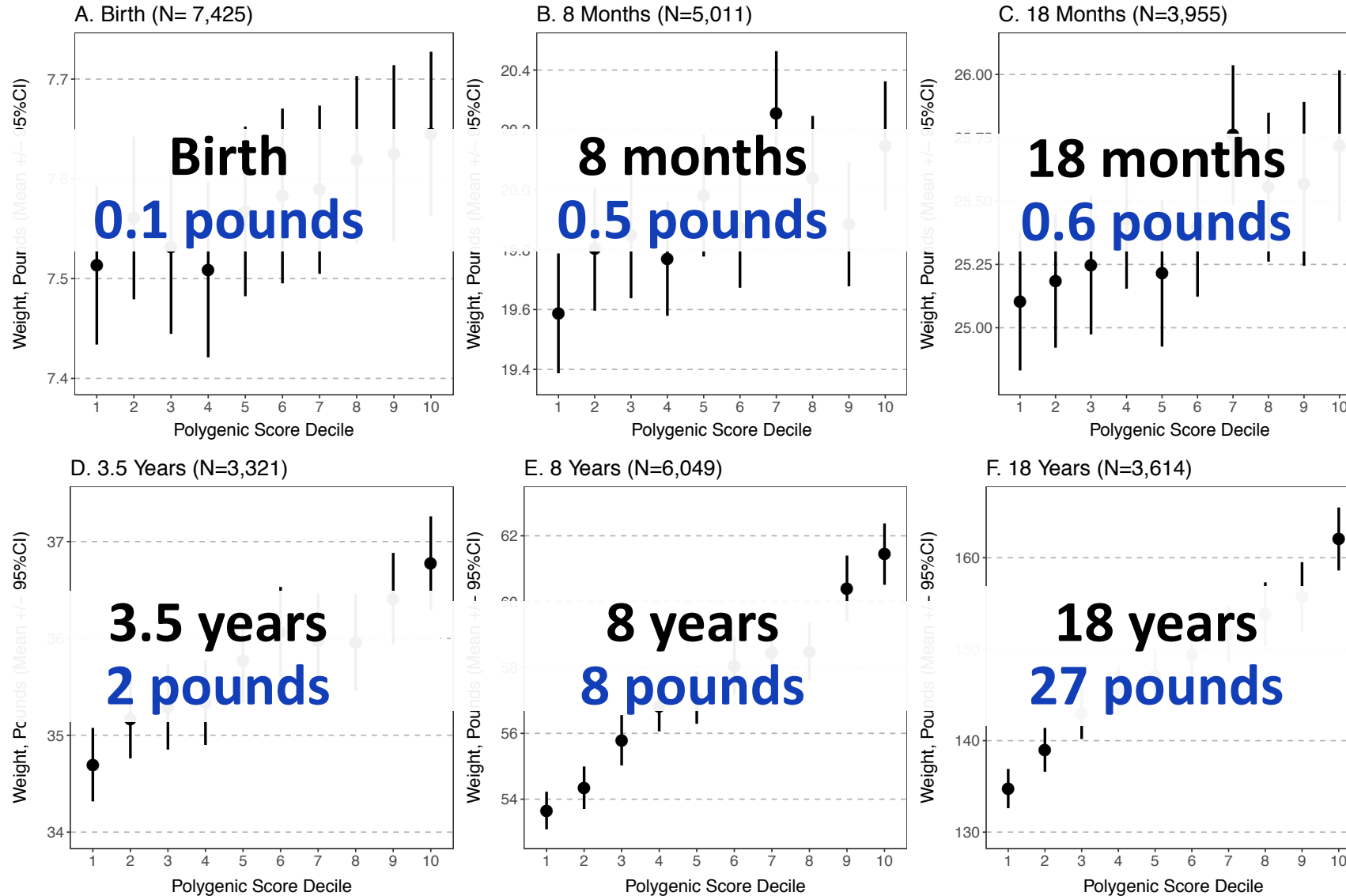
Followed birth to age 18

18 years



Impact of polygenic obesity to obesity in childhood

Birth – 18 years

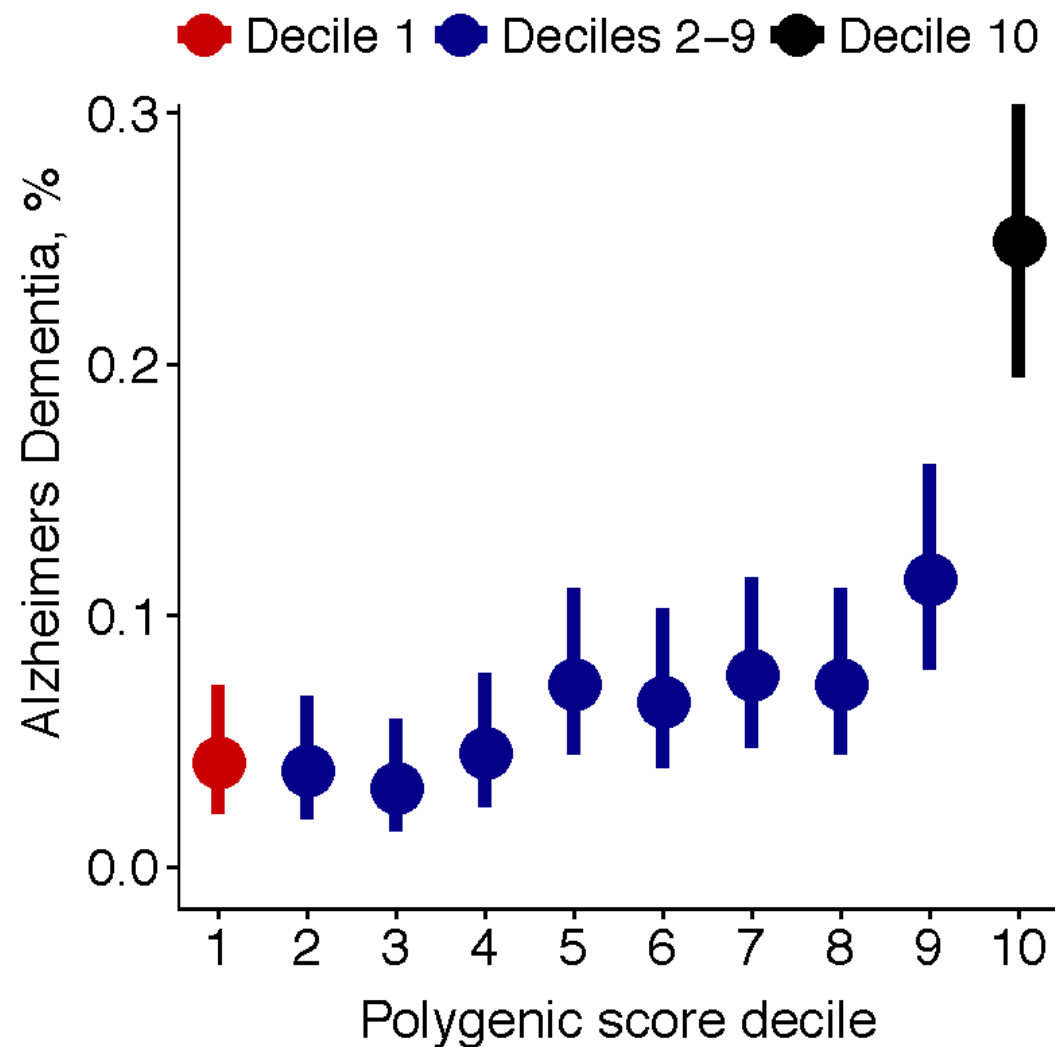


How does polygenic susceptibility to Alzheimer's dementia impact risk?

Zahid* ... Khera | *Manuscript in preparation*

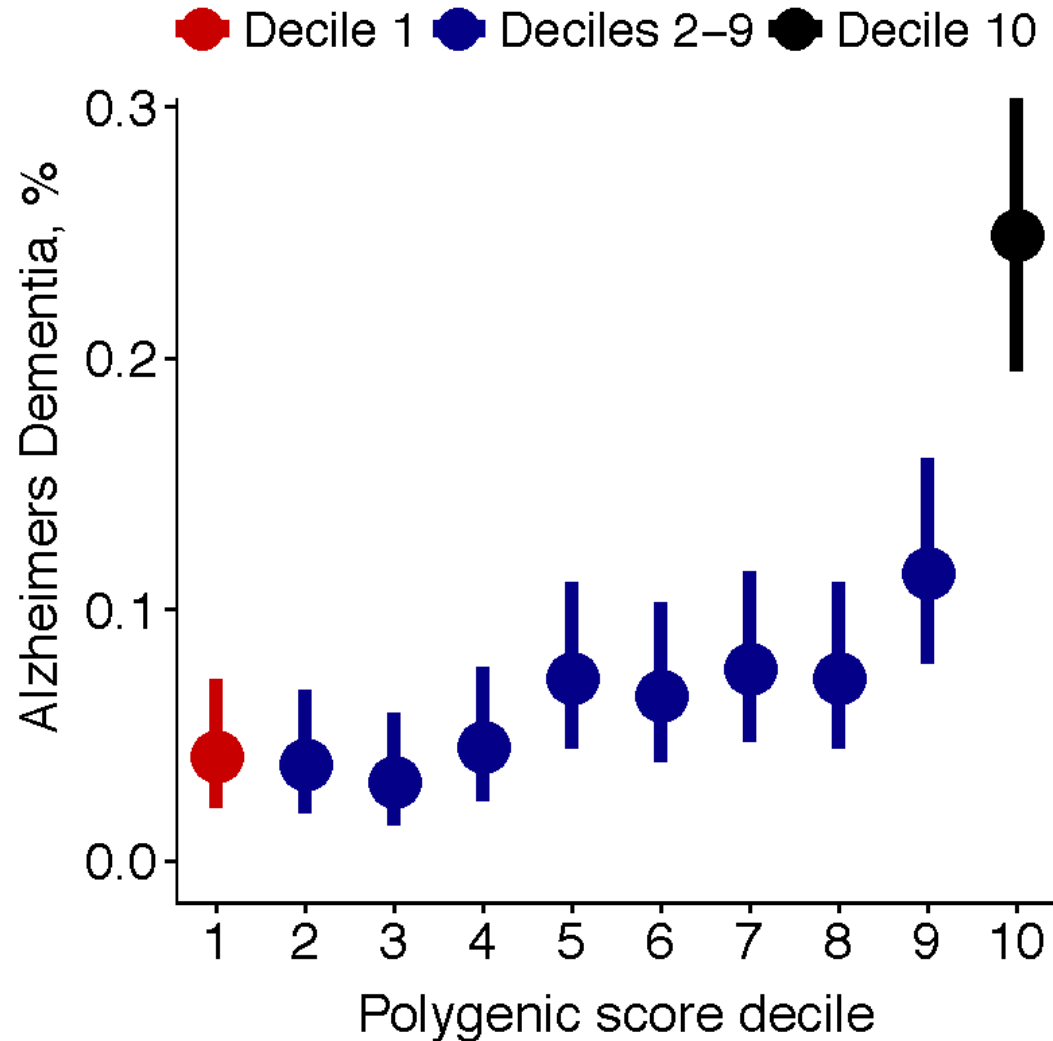
Polygenic score for Alzheimer's disease

5-fold risk gradient across deciles in middle age



Polygenic score for Alzheimer's disease

5-fold risk gradient across deciles in middle-age



ApoE locus:

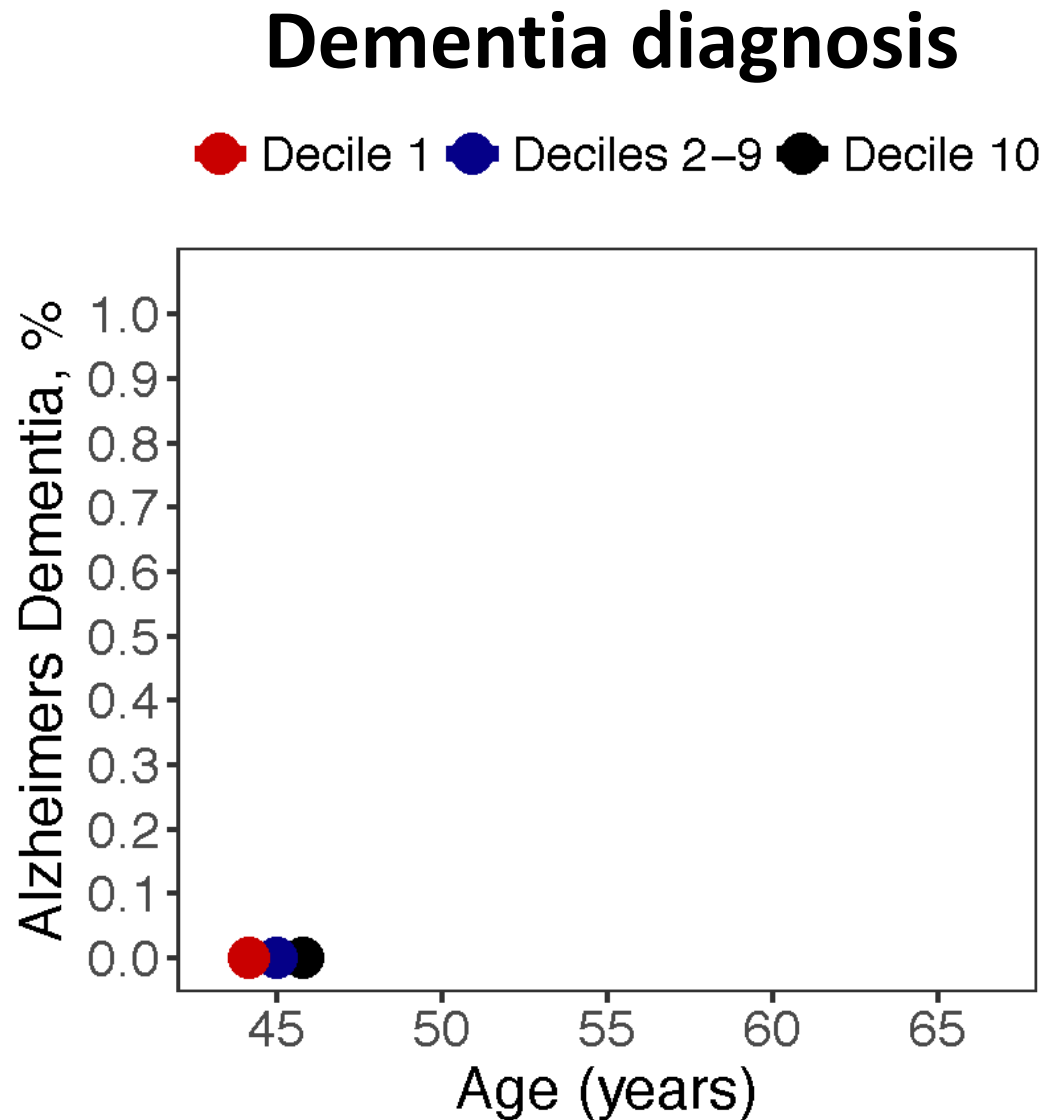
70% of predictive value

Remaining variants:

30% of predictive value

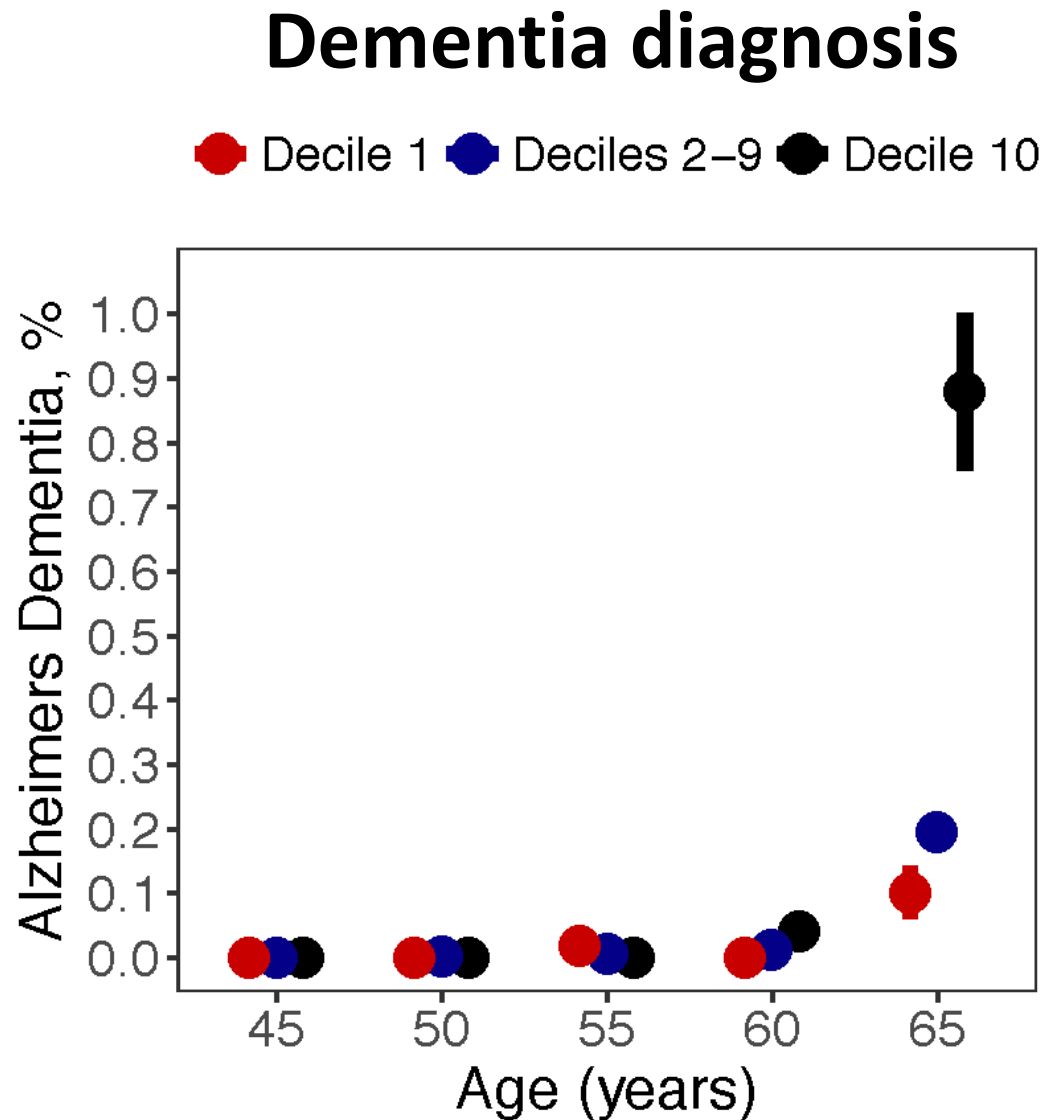
Polygenic score for Alzheimer's disease

Impact increases with age



Polygenic score for Alzheimer's disease

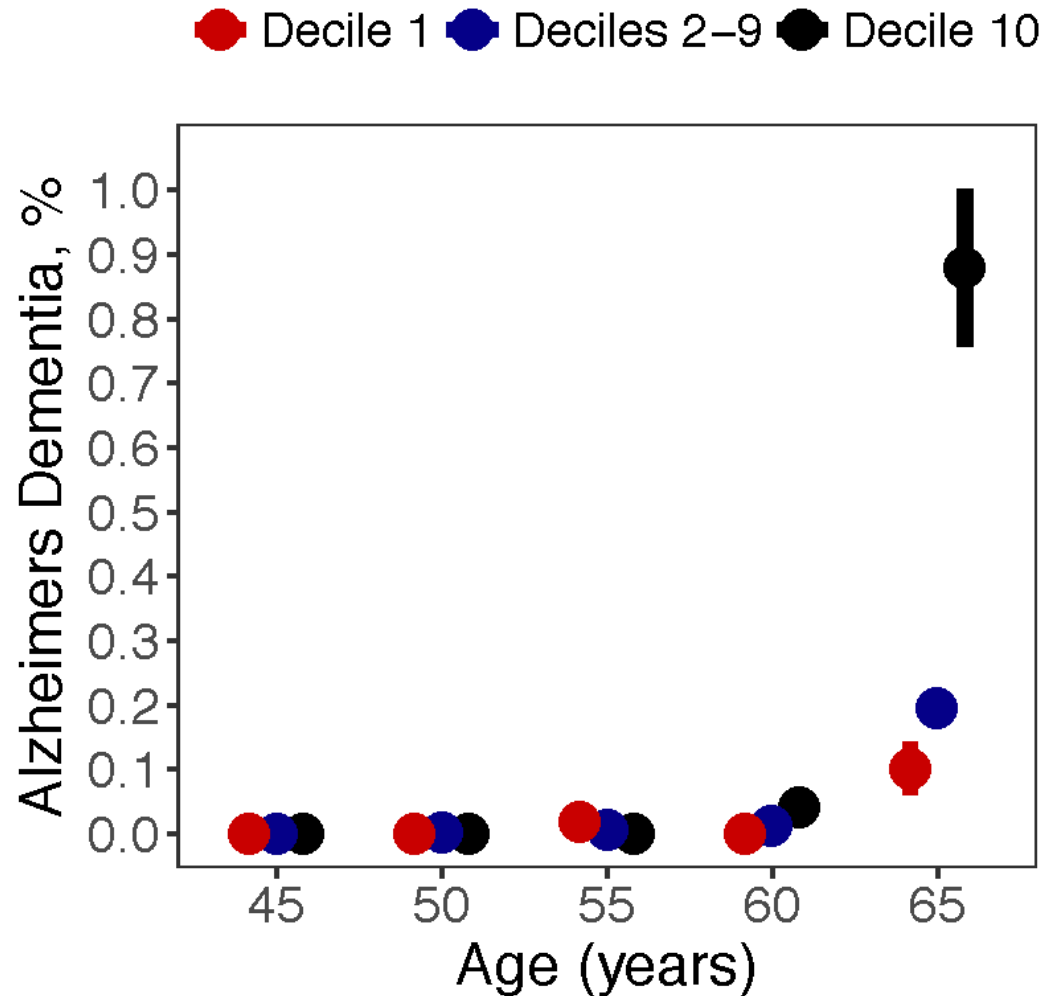
Impact increases with age



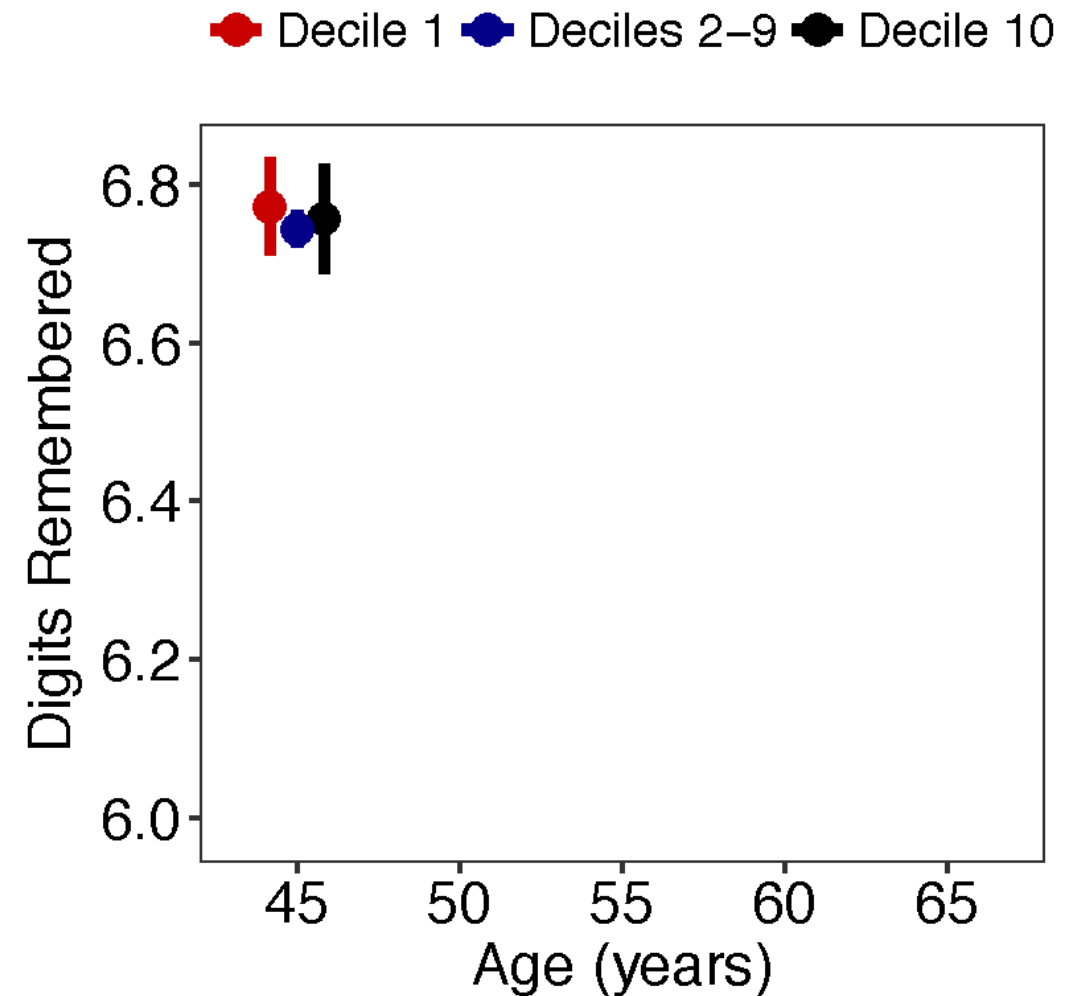
Polygenic score for Alzheimer's disease

Impact increases with age

Dementia diagnosis



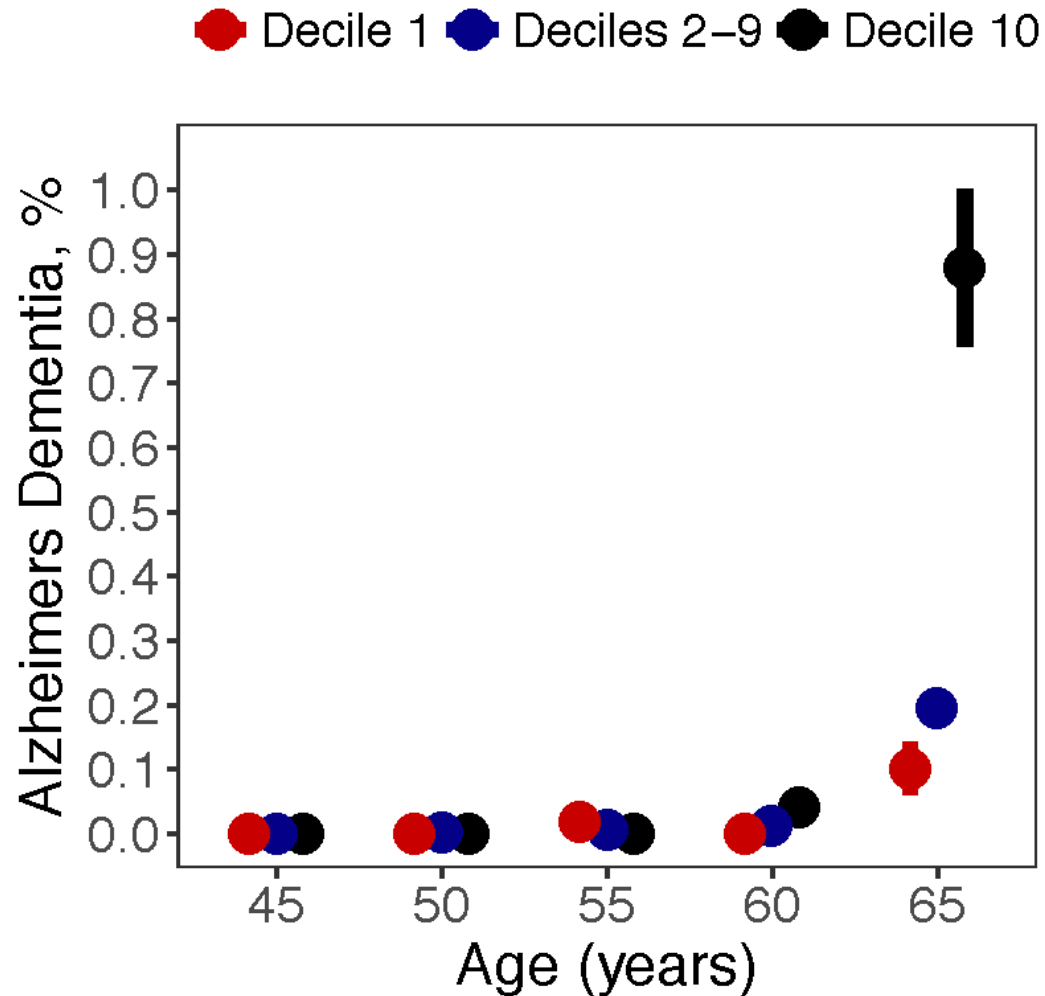
Cognitive function



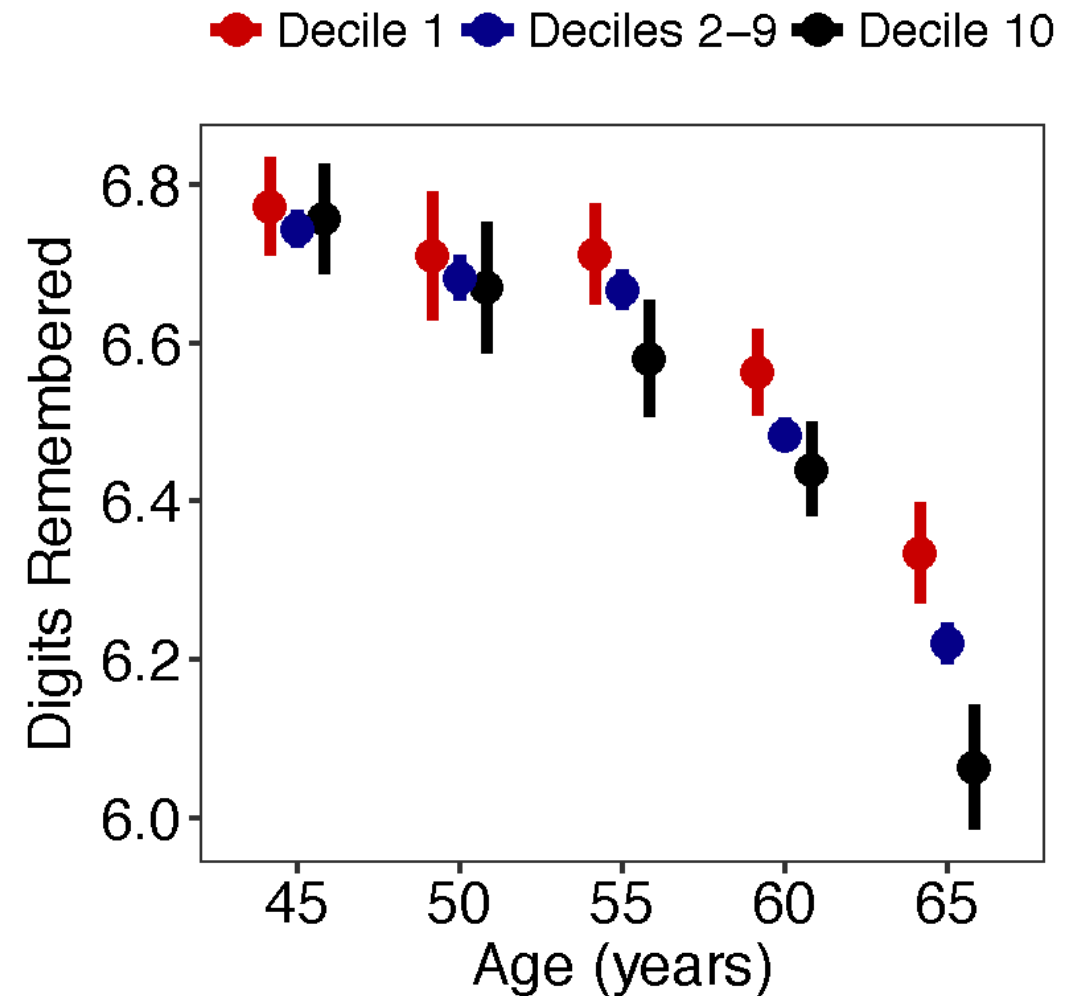
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Dementia diagnosis



Cognitive function



Polygenic scores enable ‘**genome-interpretation**’ from the **time of birth** for a range of important diseases and they **will continue to improve** in coming years

Polygenic scores enable ‘**genome-interpretation**’ from the **time of birth** for a range of important diseases and they **will continue to improve** in coming years

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green¹, Mark S. Guyer¹ & National Human Genome Research Institute*

