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The intricate relation between genetics and lifestyle in the etiology of dementia

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Disclosures in last 2 years

Ad hoc consultancy for BioGen Inc. (discontinued)

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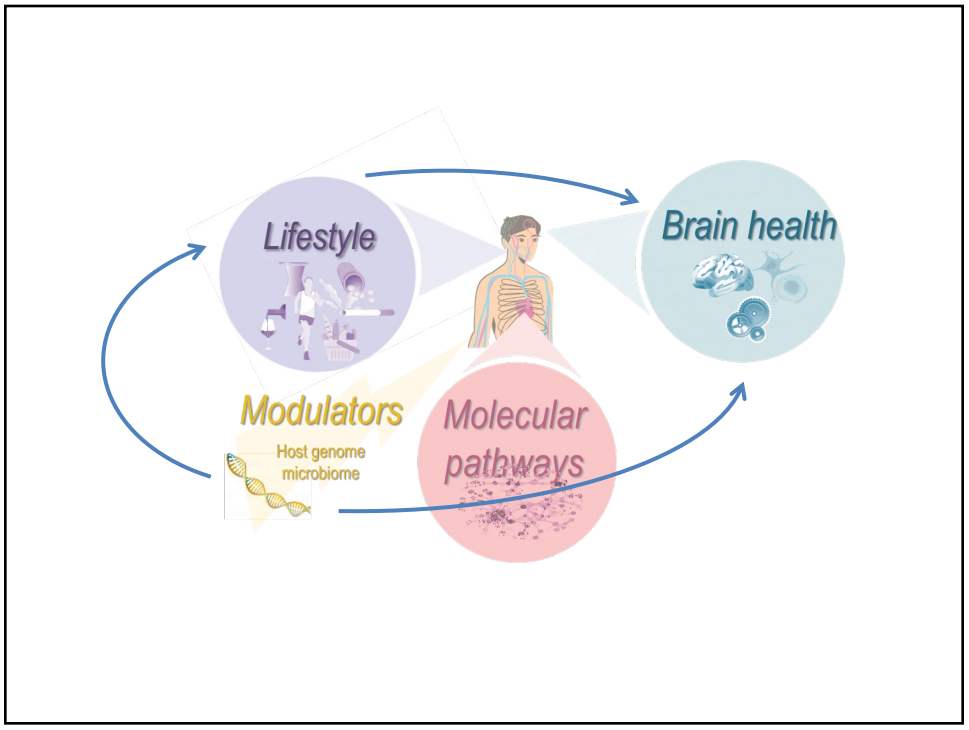

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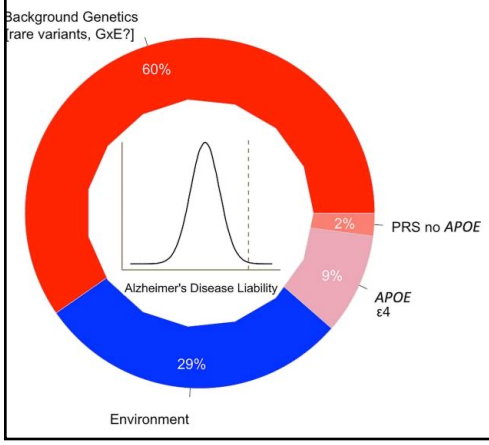
JAMA Network Open.
https://doi.org/10.1093/braincomms/fcab308 BRAIN COMMUNICATIO
BRAIN COMMUNICATIONS

Measuring heritable contributions to Alzheimer's disease: polygenic risk score analysis with twins

Ida K. Karlsson,[1,2] Valentina Escott-Price,[3] Margaret Gatz,[1,4] John Hardy,[5,6,7,8,9] Nancy L. Pedersen,[1,10] Maryam Shoai[5,6] and Chandra A. Reynolds[11]



Original Investigation | Neurology

Variation in Population Attributable Fraction of Dementia Associated With Potentially Modifiable Risk Factors by Race and Ethnicity in the US

Mark Lee, MA; Eric Whitsel, MD, MPH; Christy Avery, PhD; Timothy M. Hughes, PhD; Michael E. Griswold, PhD; Sanaz Sedaghat, PhD; Rebecca F. Gottesman, MD, PhD; Thomas H. Mosley, PhD; Gerardo Heiss, PhD; Pamela L. Lutsey, PhD, MPH

Risk factor	Total population	
	Prevalence, %	PAF, % (95% CI)
Less education	10.7	6.0 (2.7-9.8)
Hearing loss	10.8	8.9 (3.9-15.7)
TBI	17.1	12.0 (8.5-17.0)
Hypertension	42.2	20.2 (6.3-34.4)
Excessive alcohol	3.6	0.7 (0.2-1.1)
Obesity	44.0	20.9 (13.0-28.8)
Smoking	8.5	4.9 (1.3-9.3)
Depression	7.4	6.2 (3.9-9.0)
Social isolation	11.9	6.7 (3.7-9.2)
Physical inactivity	62.8	20.1 (9.1-29.6)
Diabetes	28.6	12.5 (8.6-18.4)
Air pollution	22.8	2.2 (1.6-2.4)
Combined factors[a]	NA	41.0 (22.7-55.9)

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Genomics and lifestyle

- Unraveling etiology and pathways
  - Discovering novel genes and GxE interaction
  - Establishing causality
- Identification of persons at increased risk
  - Trial design
  - Preventive intervention

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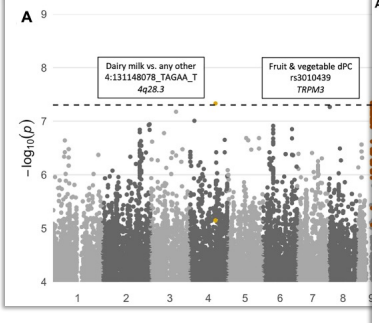
Discovering novel genes and GxE interaction

Genome-wide gene–diet interact
Biobank identifies novel effects

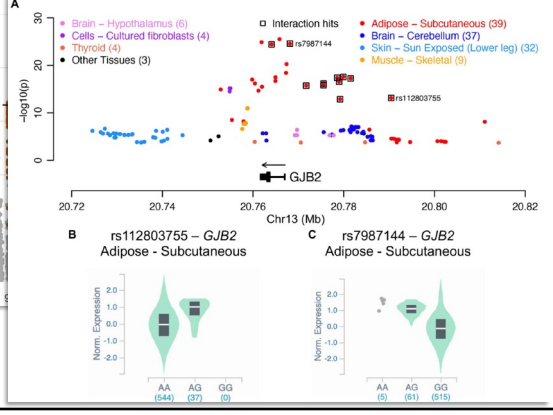
Kenneth E. Westerman[1,2,3], Jenkai Miao[4], Dar
Jose C. Florez[2,3,9], Han Chen[10,11], Alisa K. Mar
Joanne B. Cole[2,4,9,*]



RESEARCH ARTICLE

Genome-wide association study of fish oil supplementation on lipid traits in 81,246 individuals reveals new gene-diet interaction loci

Michael Francis[1], Changwei Li[2], Yitang Sun[3], Jingqi Zhou[3], Xiang Li[2], J. Thomas Brenna[4,5,6], Kaixiong Ye[1,3]*



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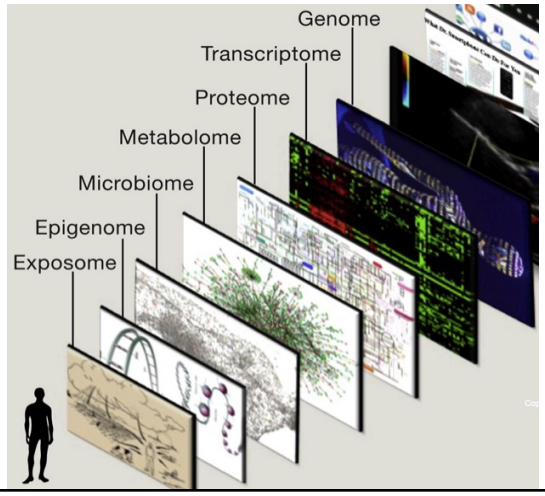
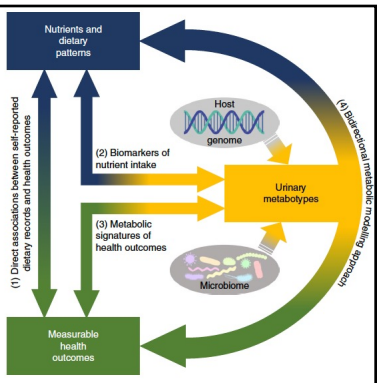
ARTICLES
https://doi.org/10.1038/s43016-020-0093-y
nature food

Nutriome–metabolome relationships provide insights into dietary intake and metabolism

Joram M. Posma[1,2], Isabel Garcia-Perez[3], Gary Frost[3], Ghadeer S. Aljuraiban[4,5], Queenie Chan[5,6], Linda Van Horn[7], Martha Daviglus[8], Jeremiah Stamler[7], Elaine Holmes[3,9,10,11] ✉, Paul Elliott[2,5,6,9,12,13] ✉ and Jeremy K. Nicholson[10,11] ✉





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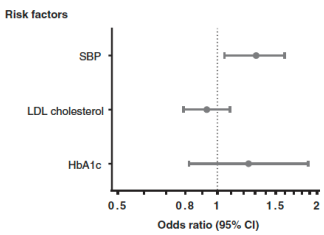
Mendelian Randomization

DOI: 10.1002/alz.12320
RESEARCH ARTICLE
Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Midlife vascular risk factors and risk of incident dementia: Longitudinal cohort and Mendelian randomization analyses in the UK Biobank

Rainer Malik[1] | Marios K. Georgakis[1] | Julia Neitzel[1] | Kristiina Rannikmäe[2] | Michael Ewers[1] | Sudha Seshadri[3] | Cathie L.M. Sudlow[4,5] | Martin Dichgans[1,6,7]



	OR (95% CI)	p-value	p-het
SBP	1.31 [1.05-1.60]	0.013	0.806
LDL cholesterol	0.93 [0.79-1.09]	0.370	0.948
HbA1c	1.24 [0.82-1.88]	0.295	0.797

1 SD increase = 1.18, 95% CI [0.82–1.54], $P = 0.12$). The number of independent genetic variants as instruments for smoking, BMI, physical activity, and diet was 126, 941, 3, and 12, respectively. There were no significant associations between smoking, BMI, physical activity, or diet in IVW or alternative MR methods (Table S13). Scatter plots for

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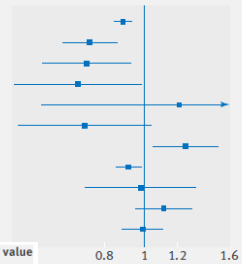
Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis

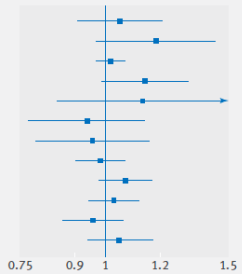
Susanna C Larsson,[1,2] Matthew Traylor,[2] Rainer Malik,[3] Martin Dichgans,[3,4,5] Stephen Burgess,[6,7] Hugh S Markus,[2] for the CoSTREAM Consortium, on behalf of the International Genomics of Alzheimer's Project

Risk factor	No of SNPs	Odds ratio (95% CI)	P value
Years of education	152	0.89 (0.84 to 0.93)	2.4×10^{-6}
College/university	32	0.74 (0.63 to 0.86)	8.0×10^{-5}
Intelligence	16	0.73 (0.57 to 0.93)	0.01
Smoking quantity	4	0.69 (0.49 to 0.99)	0.04
Smoking quantity	3*	1.21 (0.56 to 2.61)	0.62
Alcohol consumption	3	0.72 (0.50 to 1.04)	0.08
Coffee consumption	5	1.26 (1.05 to 1.51)	0.01
25-hydroxyvitamin D	4	0.92 (0.85 to 0.98)	0.01
Serum folate	2	0.98 (0.72 to 1.33)	0.89
Serum vitamin B12	7	1.11 (0.95 to 1.30)	0.18
Total homocysteine	18	0.99 (0.88 to 1.11)	0.86



Ids ratio of Alzheimer's disease per genetically predicted increase in each risk factor

Risk factor	No of SNPs	Odds ratio (95% CI)	P value
BMI	76*	1.05 (0.91 to 1.21)	0.51
Waist to hip ratio	38	1.18 (0.97 to 1.45)	0.10
Type 2 diabetes	50	1.02 (0.97 to 1.07)	0.49
Fasting glucose	36	1.14 (0.99 to 1.32)	0.07
Fasting insulin	19	1.13 (0.85 to 1.51)	0.40
Systolic blood pressure	93	0.94 (0.77 to 1.14)	0.51
Diastolic blood pressure	105	0.96 (0.79 to 1.16)	0.65
HDL cholesterol	70*	0.98 (0.90 to 1.07)	0.64
LDL cholesterol	56*	1.07 (0.98 to 1.17)	0.14
Total cholesterol	73*	1.03 (0.94 to 1.12)	0.54
Triglycerides	40	0.96 (0.87 to 1.06)	0.40
C reactive protein	17*	1.04 (0.94 to 1.17)	0.44



Odds ratio of Alzheimer's disease per genetically predicted increase in each risk factor

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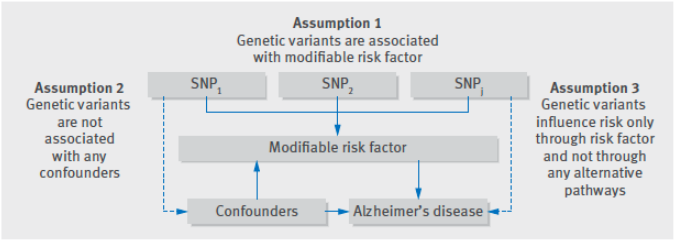
Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis

Susanna C Larsson,[1,2] Matthew Traylor,[2] Rainer Malik,[3] Martin Dichgans,[3,4,5] Stephen Burgess,[6,7] Hugh S Markus,[2] for the CoSTREAM Consortium, on behalf of the International Genomics of Alzheimer's Project



Nature as a Trialist?

Deconstructing the Analogy Between Mendelian Randomization and Randomized Trials

Sonja A. Swanson,[a,b] Henning Tiemeier,[a,c,d] M. Arfan Ikram,[a] and Miguel A. Hernán[b,e,f]

(*Epidemiology* 2017;28: 653–659)

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Preventive interventions

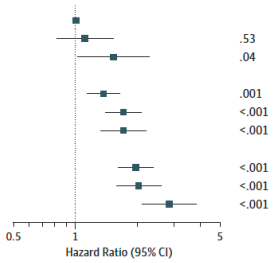
JAMA | Original Investigation

Association of Lifestyle and Genetic Risk With Incidence of Dementia

Ilianna Lourida, PhD; Eilis Hannon, PhD; Thomas J. Littlejohns, PhD; Kenneth M. Langa, MD, PhD; Elina Hyppönen, PhD; Elżbieta Kuźma, PhD; David J. Llewellyn, PhD

Figure. Risk of Incident Dementia According to Genetic and Lifestyle Risk

Subgroup	Total No. of Participants	No. of Cases of Dementia/ Person-Years	Hazard Ratio (95% CI)	P Value
Low genetic risk				
Favorable lifestyle	26856	151/211986	1 [Reference]	
Intermediate lifestyle	9114	57/72342	1.11 (0.81-1.52)	.53
Unfavorable lifestyle	3165	29/24460	1.52 (1.02-2.26)	.04
Intermediate genetic risk				
Favorable lifestyle	80290	635/633405	1.36 (1.14-1.63)	.001
Intermediate lifestyle	27703	280/219777	1.70 (1.39-2.08)	<.001
Unfavorable lifestyle	9603	99/74005	1.70 (1.31-2.19)	<.001
High genetic risk				
Favorable lifestyle	26407	298/208769	1.95 (1.60-2.38)	<.001
Intermediate lifestyle	9380	111/74652	2.02 (1.57-2.58)	<.001
Unfavorable lifestyle	3373	60/26039	2.83 (2.09-3.83)	<.001



CONCLUSIONS AND RELEVANCE Among older adults without cognitive impairment or dementia, both an unfavorable lifestyle and high genetic risk were significantly associated with higher dementia risk. A favorable lifestyle was associated with a lower dementia risk among participants with high genetic risk.

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LETTERS
https://doi.org/10.1038/s41591-019-0547-7

nature medicine

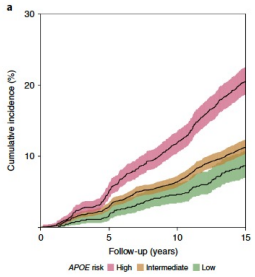
Genetic predisposition, modifiable-risk-factor profile and long-term dementia risk in the general population

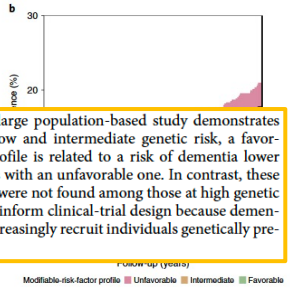
Silvan Licher[1*], Shahzad Ahmad[1], Hata Karamujić-Čomić[1], Trudy Voortman[1], Maarten J. G. Leening[1,2,3], M. Arfan Ikram[1] and M. Kamran Ikram[1,4*]

Table 3 | Risk of incident dementia participants stratified on both their *APOE*-risk and modifiable-risk-factor profiles

APOE-related risk	Risk-factor profile	*N*/*n*	HR (95% CI)
Low (ε2ε2 or ε2ε3)	Favorable	568/44	Reference
	Intermediate	224/23	1.14 (0.66-1.96)
	Unfavorable	95/18	2.51 (1.40-4.48)
	P for trend		0.0059
Intermediate (ε3ε3)	Favorable	2,453/253	Reference
	Intermediate	884/139	1.27 (1.02-1.57)
	Unfavorable	381/64	1.39 (1.04-1.85)
	P for trend		0.0087
High (ε2ε4, ε3ε4 or ε4ε4)	Favorable	1,132/241	Reference
	Intermediate	443/97	1.00 (0.79-1.28)
	Unfavorable	172/36	1.05 (0.73-1.50)
	P for trend		0.8300

This model was adjusted for age, sex and education. *N*, number of individuals at risk; *n*, number of dementia cases during follow-up.





In conclusion, this large population-based study demonstrates that, among those at low and intermediate genetic risk, a favorable modifiable-risk profile is related to a risk of dementia lower than that in individuals with an unfavorable one. In contrast, these protective associations were not found among those at high genetic risk. These results may inform clinical-trial design because dementia-prevention trials increasingly recruit individuals genetically predisposed to dementia.

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UK Biobank	**Rotterdam Study**
Total sample: 196,383	Total sample: 6,352
Response rate ~10%	Response rate ~70%
Mean age at entry 65yr	Mean age at entry 69yr
Median follow-up time 8.0 years	Median follow-up time 14.1 years
Dementia diagnosis: registries, partly based on medical records	Dementia diagnosis: in-person and medical records
Healthy lifestyle: 4 factors	Healthy lifestyle: 6 factors AHA Healthy CVS 10-year CV risk
Background risk of dementia 0.9%	Background risk of dementia 14.4%

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Conclusions

The fields of genetics and lifestyle research are rapidly converging and play a role in understanding biology and identification of persons at highest risk

Addition of novel (molecular) omics layers calls for novel methods for analysis and visualization

The added value of lifestyle to offset genetic risk needs further investigation

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Thank you for your attention!

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