

Association of Lifestyle and Genetic Risk With Incidence of Dementia

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IMPORTANCE Genetic factors increase risk of dementia, but the extent to which this can be offset by lifestyle factors is unknown.

OBJECTIVE To investigate whether a healthy lifestyle is associated with lower risk of dementia regardless of genetic risk.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study that included adults of European ancestry aged at least 60 years without cognitive impairment or dementia at baseline. Participants joined the UK Biobank study from 2006 to 2010 and were followed up until 2016 or 2017.

EXPOSURES A polygenic risk score for dementia with low (lowest quintile), intermediate (quintiles 2 to 4), and high (highest quintile) risk categories and a weighted healthy lifestyle score, including no current smoking, regular physical activity, healthy diet, and moderate alcohol consumption, categorized into favorable, intermediate, and unfavorable lifestyles.

MAIN OUTCOMES AND MEASURES Incident all-cause dementia, ascertained through hospital inpatient and death records.

RESULTS A total of 196 383 individuals (mean [SD] age, 64.1 [2.9] years; 52.7% were women) were followed up for 1 545 433 person-years (median [interquartile range] follow-up, 8.0 [7.4–8.6] years). Overall, 68.1% of participants followed a favorable lifestyle, 23.6% followed an intermediate lifestyle, and 8.2% followed an unfavorable lifestyle. Twenty percent had high polygenic risk scores, 60% had intermediate risk scores, and 20% had low risk scores. Of the participants with high genetic risk, 1.23% (95% CI, 1.13%–1.35%) developed dementia compared with 0.63% (95% CI, 0.56%–0.71%) of the participants with low genetic risk (adjusted hazard ratio, 1.91 [95% CI, 1.64–2.23]). Of the participants with a high genetic risk and unfavorable lifestyle, 1.78% (95% CI, 1.38%–2.28%) developed dementia compared with 0.56% (95% CI, 0.48%–0.66%) of participants with low genetic risk and favorable lifestyle (hazard ratio, 2.83 [95% CI, 2.09–3.83]). There was no significant interaction between genetic risk and lifestyle factors (P = .99). Among participants with high genetic risk, 1.13% (95% CI, 1.01%–1.26%) of those with a favorable lifestyle developed dementia compared with 1.78% (95% CI, 1.38%–2.28%) with an unfavorable lifestyle (hazard ratio, 0.68 [95% CI, 0.51–0.90]).

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.

Key Points

Question Is a healthy lifestyle associated with lower risk of dementia, regardless of genetic risk?

Findings In this retrospective cohort study that included 196 383 participants of European ancestry aged at least 60 years without dementia at baseline, participants with a high genetic risk and unfavorable lifestyle score had a statistically significant hazard ratio for incident all-cause dementia of 2.83 compared with participants with a low genetic risk and favorable lifestyle score. A favorable lifestyle was associated with a lower risk of dementia and there was no significant interaction between genetic risk and healthy lifestyle.

Meaning A healthy lifestyle was associated with lower risk of dementia among participants with low or high genetic risk.

Table 1. Baseline Characteristics of Participants in a Study of the Association of Lifestyle and Genetic Risk With Incidence of Dementia

Characteristic	No. (%) ^a	
	Incident Dementia (n = 1769)	No Incident Dementia (n = 194 614)
Age, mean (SD), y	65.8 (2.7)	64.1 (2.8)
Sex		
Male	979 (55.3)	91 961 (47.3)
Female	790 (44.7)	102 653 (52.8)
Education ^{b,c}		
Higher	550 (31.1)	80 874 (41.6)
Upper secondary	79 (4.5)	8899 (4.6)
Lower secondary	264 (14.9)	31 337 (16.1)
Vocational	179 (10.1)	20 118 (10.3)
Other	697 (39.4)	53 385 (27.4)
Socioeconomic status quintile ^{c,d}		
1 (least deprived)	317 (17.9)	38 927 (20.0)
2–4	950 (53.7)	116 911 (60.1)
5 (most deprived)	502 (28.4)	38 776 (19.9)
Depressive symptoms in last 2 weeks ^e	444 (25.1)	34 516 (17.7)
Healthy lifestyle factors ^f		
No current smoking	1580 (89.3)	178 631 (91.8)
Regular physical activity	1334 (75.4)	149 037 (76.6)
Healthy diet	861 (48.7)	98 842 (50.8)
Moderate alcohol consumption	925 (52.3)	109 291 (56.2)
History of stroke ^g	203 (11.5)	7340 (3.8)
No. of healthy lifestyle factors ^h		
0	26 (1.5)	1929 (0.99)
1	188 (10.6)	16 358 (8.4)
2	516 (29.2)	53 969 (27.7)
3	674 (38.1)	77 925 (40.0)
4	365 (20.6)	44 432 (22.8)
Genetic risk category ⁱ		
Low	247 (14.0)	39 029 (20.1)
Intermediate	1038 (58.7)	116 792 (60.0)
High	484 (27.4)	38 793 (19.9)

^a Percentages may not sum to 100 because of rounding.
^b Higher education defined as college/university degree or other professional qualification; upper secondary, second/final stage of secondary education; lower secondary, first stage of secondary education; vocational, work-related practical qualifications.
^c Missing values imputed using multiple imputations by chained equations with 40 imputations.
^d Socioeconomic status assessed with the Townsend deprivation index,²⁷ which combines information on social class, employment, car availability, and housing.
^e Genetic risk categories defined according to a polygenic risk score as low (lowest quintile), intermediate (quintiles 2 to 4), and high (highest quintile).

Table 2. Risk of Incident Dementia According to Genetic Risk

Genetic Risk	Model 1 ^a			Model 2 ^b		
	Low (n = 39 276)	Intermediate (n = 117 830)	High (n = 39 277)	Low (n = 39 276)	Intermediate (n = 117 830)	High (n = 39 277)
No. of dementia cases/person-years	247/308 788	1038/927 186	484/309 460	247/308 788	1038/927 186	484/309 460
HR (95% CI)	1 [Reference]	1.37 (1.20–1.58)	1.91 (1.64–2.23)	1 [Reference]	1.38 (1.20–1.58)	1.91 (1.64–2.23)
P value		<.001	<.001		<.001	<.001
P value for trend		<.001			<.001	

Abbreviation: HR, hazard ratio.
^a Model 1: Cox proportional hazards regression adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, and first 20 principal components of ancestry; P value for trend calculated treating the genetic risk score as a continuous variable.
^b Model 2: Cox proportional hazards regression adjusted for Model 1 and weighted lifestyle categories; P value for trend calculated treating the genetic risk score as a continuous variable.

Table 3. Risk of Incident Dementia According to Lifestyle Categories

Healthy Lifestyle Category ^{a,d}	Model 1 ^a			Model 2 ^b		
	Favorable (n = 133 655)	Intermediate (n = 46 285)	Unfavorable (n = 16 153)	Favorable (n = 133 655)	Intermediate (n = 46 285)	Unfavorable (n = 16 153)
No. of dementia cases/person-years ^d	1095/1 054 159	460/366 771	188/124 503	1095/1 054 159	460/366 771	188/124 503
HR (95% CI)	1 [Reference]	1.17 (1.04–1.31)	1.35 (1.15–1.58)	1 [Reference]	1.17 (1.04–1.31)	1.34 (1.15–1.57)
P value		.009	<.001		.009	<.001
P value for trend		<.001			<.001	

Abbreviation: HR, hazard ratio.
^a Model 1: Cox proportional hazards regression adjusted for age, sex, education, socioeconomic status, relatedness, and first 20 principal components of ancestry; P value for trend calculated treating the healthy lifestyle score as a continuous variable.
^b Model 2: Cox proportional hazards regression adjusted for Model 1, genetic risk categories and number of alleles included in the polygenic risk score.
^c Weighted healthy lifestyle score was categorized as favorable (68.1%), intermediate (23.6%), and unfavorable (8.2%) based on the distribution of the unweighted lifestyle score.
^d Number of observations varies among imputations.

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

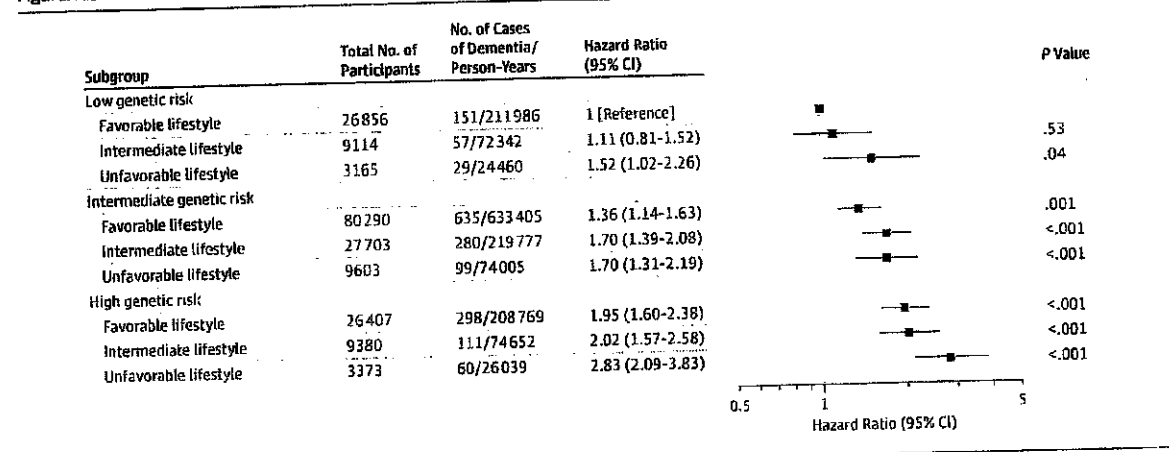


Table 4. Risk of Incident Dementia According to Healthy Lifestyle Category Within Each Genetic Risk Category^a

Healthy Lifestyle Category ^b	Low			Intermediate			High		
	Favorable (n = 26 856)	Intermediate (n = 9114)	Unfavorable (n = 3165)	Favorable (n = 80 290)	Intermediate (n = 27 703)	Unfavorable (n = 9603)	Favorable (n = 26 407)	Intermediate (n = 9380)	Unfavorable (n = 3373)
No. of dementia cases/person-years ^b	151/211 986	57/72 342	29/24 460	635/633 405	280/219 777	99/74 005	298/208 769	111/74 652	60/26 039
HR (95% CI)	0.69 (0.46–1.04)	0.75 (0.48–1.19)	1 [Reference]	0.80 (0.65–0.99)	1.00 (0.79–1.26)	1 [Reference]	0.68 (0.51–0.90)	0.71 (0.51–0.97)	1 [Reference]
P value	.07	.22		.04	1.00		.008	.03	
P value for trend		.11			.003			.03	

Abbreviation: HR, hazard ratio.
^a Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, and first 20 principal components of ancestry.
^b Number of observations varies among imputations.