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# Association of Lifestyle and Genetic Risk With Incidence of Dementia

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 Supplemental content

**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.

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Both genetic and lifestyle factors play a role in determining individual risk of Alzheimer disease and other dementia subtypes.<sup>1</sup> Mutations in the amyloid precursor protein (*APP*; OMIM:104760), presenilin 1 (*PSEN1*; OMIM:104311), and presenilin 2 (*PSEN2*; OMIM:600759) genes can cause early-onset Alzheimer disease, although this accounts for a small percentage of cases.<sup>2</sup> Most dementia cases occur sporadically in older adults in whom multiple genes influence risk. The  $\epsilon 4$  allele of the apolipoprotein E gene (*APOE*; OMIM:107741) is known to increase the risk of Alzheimer disease.<sup>3,4</sup> A meta-analysis of genome-wide association studies identified additional loci associated with the risk of late-onset Alzheimer disease in participants of European ancestry.<sup>3</sup> Polygenic risk scores combining multiple risk alleles for Alzheimer disease are predictive of incident all-cause dementia and provide a quantitative measure of genetic dementia risk.<sup>5,6</sup>

There is considerable evidence that individuals who avoid smoking tobacco, are physically active, drink alcohol in moderation, and have a healthy diet have a lower dementia risk.<sup>7-10</sup> Studies have combined lifestyle factors to create a composite lifestyle score to investigate the relationship between lifestyle factors and other health conditions, such as cardiovascular disease and diabetes.<sup>11,12</sup> It is possible that genetic risk can be offset by lifestyle factors. Studies that examined whether the risk reduction associated with adherence to a healthy lifestyle varied on the basis of *APOE*  $\epsilon 4$  allele haplotype have yielded inconsistent results; however, statistical power was limited in these studies and other genetic factors were not incorporated.<sup>13,14</sup>

The purpose of this study was to use data from a large population-based cohort to investigate the hypothesis that adherence to a healthy lifestyle may offset genetic risk for dementia.

## Methods

This retrospective cohort study is based on data from the UK Biobank study<sup>15</sup> that received approval from the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee. All participants provided informed consent through electronic signature at baseline assessment.

### Study Population

The UK Biobank is a population-based cohort of more than 500 000 participants who attended 1 of 22 assessment centers across the United Kingdom between 2006 and 2010.<sup>15</sup> Analyses were restricted to individuals aged at least 60 years at baseline (because the majority of incident dementia cases occur in older adults) and individuals with genetic information available. Participants with self-reported prevalent cognitive impairment or dementia at baseline or prevalent dementia diagnosis identified via hospital inpatient records were excluded.

### Polygenic Risk Score

A polygenic risk score that captured an individual's load of common genetic variants associated with Alzheimer disease and dementia risk was constructed (full details in eMethods in

## 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.

Supplement 1). The score was based on Alzheimer disease statistics based on genome-wide association studies of individuals of European ancestry.<sup>3</sup> Therefore, the present study was restricted to individuals whose self-reported racial/ethnic background was white (British, Irish, or other white background). Single-nucleotide polymorphisms (SNPs) were selected using “clumped” results (ie, the most significant variant per linkage disequilibrium block) from a previously published Alzheimer disease genome-wide association study,<sup>3</sup> restricting the selection to SNPs that are common and available in the UK Biobank. The polygenic risk score was calculated across all SNPs associated with Alzheimer disease with a *P* value less than .50 as a threshold for inclusion (*N* = 249 273; full list provided in the eAppendix in Supplement 2), because it has been established that this more comprehensive set of SNPs enhances risk prediction.<sup>16</sup> The number of associated alleles at each SNP was weighted according to the strength of their association with Alzheimer disease in the discovery genome-wide association study,<sup>3</sup> summed, and then *z*-standardized to derive a polygenic risk score for all individuals in the UK Biobank. This polygenic risk score was then categorized into low (lowest quintile), intermediate (quintiles 2 to 4), and high (highest quintile) risk.

### Healthy Lifestyle Score

A healthy lifestyle score was constructed based on 4 well-established dementia risk factors (smoking status, physical activity, diet, and alcohol consumption)<sup>7-10</sup> assessed at baseline using a touchscreen questionnaire. Participants scored 1 point for each of 4 healthy behaviors defined on the basis of national recommendations (full details in eTable 1 in Supplement 1). Smoking status was categorized as current or no current smoking. Regular physical activity was defined as meeting the American Heart Association recommendations of at least 150 minutes of moderate activity per week or 75 minutes of vigorous activity per week (or an equivalent combination)<sup>17</sup> or engaging in moderate physical activity at least 5 days a week or vigorous activity once a week. Healthy diet was based on consumption of at least 4 of 7 commonly eaten food groups following recommendations on dietary priorities for cardiometabolic health,<sup>18</sup> which are linked to

better late-life cognition and reduced dementia risk.<sup>19-21</sup> Previous studies of alcohol consumption and dementia risk support a U-shaped relationship, with moderate consumption associated with lower risk.<sup>7,22,23</sup> Therefore, moderate consumption was defined as 0 to 14 g/d for women and 0 to 28 g/d for men, with the maximum limit reflecting US dietary guidelines.<sup>24</sup> The lifestyle index scores ranged from 0 to 4, with higher scores indicating higher adherence to healthy lifestyle, and were subsequently categorized as favorable (3 or 4 healthy lifestyle factors), intermediate (2 healthy lifestyle factors), and unfavorable (0 or 1 healthy lifestyle factor) lifestyles. A weighted standardized healthy lifestyle score was then derived based on  $\beta$  coefficients of each lifestyle factor in the Cox proportional hazards regression model with all 4 lifestyle factors and adjustment for age, sex, education, socioeconomic status, third-degree relatedness, and the first 20 principal components of ancestry. The original binary lifestyle variables were multiplied by the  $\beta$  coefficients, summed, divided by the sum of the  $\beta$  coefficients, and multiplied by 100. The weighted standardized lifestyle score was categorized as favorable, intermediate, and unfavorable based on the distribution of the unweighted lifestyle score.<sup>25</sup>

### Dementia Diagnosis

All-cause dementia was ascertained using hospital inpatient records containing data on admissions and diagnoses obtained from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales. Additional cases were detected through linkage to death register data provided by the National Health Service Digital for England and Wales and the Information and Statistics Division for Scotland. Diagnoses were recorded using the *International Classification of Diseases (ICD)* coding system.<sup>26</sup> Participants with dementia were identified as having a primary/secondary diagnosis (hospital records) or underlying/contributory cause of death (death register) using *ICD-9* and *ICD-10* codes for Alzheimer disease and other dementia classifications (eTable 2 in Supplement 1).

### Covariates

All models were adjusted for age; sex; education, categorized as higher (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), or other; socioeconomic status (categories derived from Townsend deprivation index<sup>27</sup> quintiles 1, 2 to 4, and 5, combining information on social class, employment, car availability, and housing); third-degree relatedness of individuals in the sample; and the first 20 principal components of ancestry. Models including the polygenic risk score were also adjusted for the number of alleles included in the score to account for SNP-level variation.

### Statistical Analysis

Baseline characteristics of the analytic sample were summarized across dementia status as percentage for categorical

variables and mean and SD for normally distributed continuous variables. Multiple imputations by chained equations with 40 imputations (based on the proportion of observations with missing values<sup>28</sup>) were used to impute missing values. Absolute risk was calculated as the percentage of incident dementia cases occurring in a given group. The association between the polygenic risk score and individual lifestyle factors was assessed using multivariable logistic regression analysis. Cox proportional hazard regression models were used to examine the association of genetic risk categories, lifestyle categories, and the combination of genetic and lifestyle categories (9 categories with low genetic risk and favorable lifestyle as reference) with time to incident all-cause dementia. Participants were considered at risk for dementia from baseline (2006-2010) and were followed up until the date of first diagnosis, death, loss to follow-up, or the last date of hospital admission (March 31, 2017, for England; October 31, 2016, for Scotland; and February 29, 2016, for Wales), whichever came first. Moreover, an interaction between lifestyle and polygenic risk scores was tested, incidence rates per 1000 person-years were calculated, and analyses were stratified by genetic risk category. The proportionality of hazards assumption was assessed using the Schoenfeld residuals technique<sup>29</sup> and satisfied ( $P = .69$  for testing departures from proportionality in the first imputed data set).

Risk of incident dementia was investigated in sensitivity analyses using an unweighted lifestyle score and imputed and unimputed data, a weighted score and unimputed data, genetic risk quintiles, and the number of healthy lifestyle factors instead of categories. Additionally, the main model was adjusted for self-reported depressive symptoms (measured with the single screening question, "Over the past two weeks, how often have you felt down, depressed or hopeless?" and categorized as "yes" for answers "several days," "more than half the days," and "nearly every day" and "no" for the answer "not at all"<sup>30</sup>) and stroke history (binary variable categorized as "yes" if any type of stroke occurred at any time before dementia diagnosis or end of follow-up). Participants were excluded based on shared relatedness, a higher cutoff for moderate alcohol consumption ( $<38$  g/d)<sup>31</sup> was used, and potential differences in dementia risk were examined by sociodemographic factors in analyses stratified by age (late middle-aged [60-64 years] or young older adults [ $\geq 65$  years]), sex, and education (low or high, where high was defined as higher education).  $P$  values were 2-sided with statistical significance set at less than .05. All analyses were performed using Stata SE, version 15 (StataCorp).

## Results

At baseline, 502 536 participants were assessed. After excluding participants younger than 60 years ( $n = 285$  037), without genetic information ( $n = 20$  969), and with prevalent dementia ( $n = 147$ ), 196 383 participants were included in the analysis. Baseline characteristics of the participants are provided in Table 1. Over 1545 433 person-years of follow-up (median

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

| Characteristic                                   | No. (%) <sup>a</sup>         |                                    |
|--|------------------------------|------------------------------------|
|  | 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 <sup>b,c</sup>                         |                              |                                    |
| 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 <sup>c,d</sup>     |                              |                                    |
| 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 <sup>c</sup> | 444 (25.1)                   | 34 516 (17.7)                      |
| Healthy lifestyle factors <sup>c</sup>           |                              |                                    |
| 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 <sup>c</sup>                   | 203 (11.5)                   | 7340 (3.8)                         |
| No. of healthy lifestyle factors <sup>c</sup>    |                              |                                    |
| 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 <sup>e</sup>               |                              |                                    |
| Low  | 247 (14.0)                   | 39 029 (20.1)                      |
| Intermediate                                     | 1038 (58.7)                  | 116 792 (60.0)                     |
| High   | 484 (27.4)                   | 38 793 (19.9)                      |

<sup>a</sup> Percentages may not sum to 100 because of rounding.

<sup>b</sup> 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.

<sup>c</sup> Missing values imputed using multiple imputations by chained equations with 40 imputations.

<sup>d</sup> Socioeconomic status assessed with the Townsend deprivation index,<sup>27</sup> which combines information on social class, employment, car availability, and housing.

<sup>e</sup> Genetic risk categories defined according to a polygenic risk score as low (lowest quintile), intermediate (quintiles 2 to 4), and high (highest quintile).

[interquartile range] length of follow-up, 8.0 [7.4-8.6] years) there were 1769 cases of incident all-cause dementia. The polygenic risk score was normally distributed (eFigure in Supplement 1) and was not associated with any of the lifestyle factors, with the exception of physical activity (odds ratio [OR], 1.01 [95% CI, 1.00-1.02]; eTable 3 in Supplement 1). Most participants engaged in either 2 (27.7%) or 3 (40.0%) of 4 healthy lifestyle factors. For the weighted life-

style score, 68.1% were categorized as following a favorable lifestyle (scores ranging from 74-100), 23.6% followed an intermediate lifestyle (scores ranging from 51-73), and 8.2% followed an unfavorable lifestyle (scores ranging from 0-51).

Dementia risk increased monotonically across genetic risk categories. Of participants with a high genetic risk, 1.23% (95% CI, 1.13%-1.35%) developed dementia vs 0.63% (95% CI, 0.56%-0.71%) of participants with a low genetic risk (HR, 1.91 [95% CI, 1.64-2.23]; Table 2). Additional adjustment for lifestyle factors did not change these results, indicating that genetic risk for dementia was statistically independent of lifestyle factors. The same pattern of results was observed when genetic risk quintiles were used instead of categories (eTable 4 in Supplement 1).

Dementia risk also increased monotonically across lifestyle categories. Of participants with unfavorable lifestyle, 1.16% (95% CI, 1.01%-1.34%) developed dementia vs 0.82% (95% CI, 0.77%-0.87%) of participants with a favorable lifestyle (HR, 1.35 [95% CI, 1.15-1.58]; Table 3). Additional adjustment for genetic risk resulted in an HR of 1.34 (95% CI, 1.15-1.57), consistent with the independence of genetic and lifestyle risk factors. The same pattern of results was observed when the number of healthy lifestyle factors was used instead of lifestyle categories (eTable 5 in Supplement 1).

When genetic risk and lifestyle categories were combined there was a monotonic association with increasing genetic risk and an increasingly unhealthy lifestyle (Figure). Of participants with a high genetic risk and an unfavorable lifestyle, 1.78% (95% CI, 1.38%-2.28%) developed dementia vs 0.56% (95% CI, 0.48%-0.66%) of participants with low genetic risk and a favorable lifestyle (HR, 2.83 [95% CI, 2.09-3.83]). There was no significant interaction between the weighted healthy lifestyle score and the polygenic risk score ( $P = .99$ ), indicating that the association with lifestyle factors did not vary substantially on the basis of genetic risk. Incidence rates of all-cause dementia per 1000 person-years ranged from 0.71 (95% CI, 0.61-0.84) for participants with a low genetic risk and a favorable lifestyle to 2.30 (95% CI, 1.79-2.97) for participants with a high genetic risk and unfavorable lifestyle (eTable 6 in Supplement 1).

The same pattern of associations was observed in a series of sensitivity analyses with an unweighted lifestyle score in imputed and unimputed data and a weighted lifestyle score in unimputed data (eTable 7 in Supplement 1), with additional adjustment for depressive symptoms, when related participants were excluded, with a higher maximum limit for moderate alcohol consumption (eTable 8 in Supplement 1), or when results were stratified by age, sex, or educational level (eTable 9 in Supplement 1). Additional adjustment for stroke history resulted in an HR of 2.74 (95% CI, 2.03-3.71) for participants with a high genetic risk and unfavorable lifestyle compared with participants with low genetic risk and a favorable lifestyle (eTable 8 Supplement 1).

Further analyses stratified by genetic risk category with unfavorable lifestyle as the reference group confirmed that favorable lifestyle was associated with a lower dementia risk across genetic groups (Table 4). Among participants with high genetic risk, 1.13% (95% CI, 1.01%-1.26%) of participants with

**Table 2. Risk of Incident Dementia According to Genetic Risk**

| Genetic Risk                       | Model 1 <sup>a</sup> |                            |                   | Model 2 <sup>b</sup> |                            |                   |  |
|------------------------------------|----------------------|----------------------------|-------------------|----------------------|----------------------------|-------------------|--|
|                                    | 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.

<sup>a</sup> 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.

<sup>b</sup> 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 <sup>c,d</sup>       | Model 1 <sup>a</sup>    |                           |                          | Model 2 <sup>b</sup>    |                           |                          |  |
|---|-------------------------|---------------------------|--------------------------|-------------------------|---------------------------|--------------------------|--|
|   | 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 <sup>d</sup> | 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.

<sup>a</sup> 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.

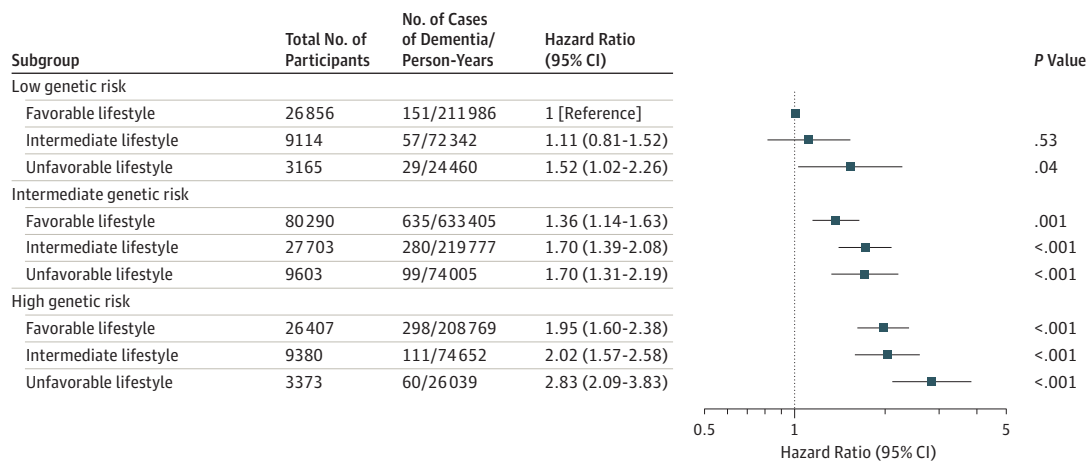
P value for trend calculated treating the healthy lifestyle score as a continuous variable.

<sup>c</sup> 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.

<sup>b</sup> Model 2: Cox proportional hazards regression adjusted for Model 1, genetic risk categories and number of alleles included in the polygenic risk score;

<sup>d</sup> Number of observations varies among imputations.

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



a favorable lifestyle developed dementia compared with 1.78% (95% CI, 1.38%-2.28%) with an unfavorable lifestyle (HR, 0.68 [95% CI, 0.51-0.90]).

high genetic risk and unfavorable lifestyle had a significantly higher risk of incident dementia compared with participants with low genetic risk and a favorable lifestyle. There was no significant interaction between genetic risk and healthy lifestyle, and a favorable lifestyle was associated with a lower risk of dementia regardless of genetic risk.

### Discussion

Genetic risk and healthy lifestyle were independently associated with risk of incident all-cause dementia. Participants with

The levels and differences in absolute risk for dementia across genetic risk and lifestyle categories are similar to those reported for stroke in a 2018 analysis using UK Biobank data.<sup>12</sup>

Table 4. Risk of Incident Dementia According to Healthy Lifestyle Category Within Each Genetic Risk Category<sup>a</sup>

| Healthy Lifestyle Category <sup>b</sup>         | 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 <sup>b</sup> | 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.

<sup>a</sup> Adjusted for age, sex, education, socioeconomic status, relatedness, number of alleles included in the polygenic risk score, and first 20 principal components of ancestry.

<sup>b</sup> Number of observations varies among imputations.

The absolute risk reduction for dementia of a favorable lifestyle compared with an unfavorable lifestyle among the high genetic risk group was 0.65%. This risk reduction implies that, if lifestyle is causal, 1 case of dementia would be prevented for each 121 individuals per 10 years with high genetic risk who improved their lifestyle from unfavorable to favorable.

To our knowledge, no previous study has investigated the association between a combination of lifestyle factors and multiple genetic risk factors and dementia incidence. Two studies have investigated whether the risk reduction associated with adherence to a healthy lifestyle is modified by *APOE*  $\epsilon$ 4 allele status.<sup>13,14</sup> The first study<sup>13</sup> of Finnish adults using data from the Cardiovascular Risk Factors, Aging, and Dementia study observed a significant association between an unfavorable lifestyle compared with a favorable lifestyle in midlife and all-cause dementia risk in late-life in 452 *APOE*  $\epsilon$ 4 allele carriers (OR for the fourth vs the first quartile, 11.42 [95% CI, 1.94-67.07]). Results were not given for the 832 *APOE*  $\epsilon$ 4 allele noncarriers, although they were stated to be nonsignificant (where  $P < .05$  indicated statistical significance).<sup>13</sup> Another study<sup>14</sup> of Japanese-American men based on data from the Honolulu-Asia Aging Study found the association between a favorable lifestyle vs unfavorable lifestyle in midlife and all-cause dementia risk in late-life was not significant in 627 male *APOE*  $\epsilon$ 4 allele carriers (OR for all 4 lifestyle factors vs 0 lifestyle factors, 0.98 [95% CI, 0.35-2.69]). However, the same association was significant in 2753 male *APOE*  $\epsilon$ 4 allele noncarriers (OR for all 4 lifestyle factors vs 0 lifestyle factors, 0.36 [95% CI, 0.15-0.84]).<sup>14</sup> These studies with inconsistent results had limited statistical power, making their findings difficult to interpret. Compared with previous studies, the present study is an order of magnitude larger and incorporates a much more comprehensive indicator of genetic risk.

A wide range of mechanisms has been proposed to explain why genetic and lifestyle factors are associated with dementia risk. Common genetic variants associated with Alzheimer disease may affect the immune response, regulation of endocytosis, cholesterol transport, and protein ubiquitination.<sup>32</sup> Healthy lifestyle may contribute to dementia risk through cardiovascular and cerebrovascular mechanisms, including reduced oxidative damage, antithrombotic and anti-inflammatory effects, and increased cerebral blood flow.<sup>7,8,18,33</sup> However, in the

present study there was no suggestion of mediation on the basis of stroke history.

### Limitations

This study has several limitations. First, unlike the genetic variants, adherence to a healthy lifestyle was not randomly assigned. Second, the lifestyle score has not been independently validated to indicate a high-risk lifestyle outside of this study. Third, although analyses were adjusted for known potential sources of bias and participants were followed up for a median of 8 years, the possibility of unmeasured confounding and reverse causation remains. Fourth, lifestyle factors were self-reported and some cases of dementia are not recorded in medical records or death registers.<sup>34</sup> However, misclassification errors are likely to have biased these findings toward the null. Additional variants associated with dementia are likely to be identified in future genome-wide association studies, and these variants may prove useful in further refining estimates of genetic risk. Fifth, other lifestyle or environmental factors may also play a role in determining dementia risk. Sixth, this sample was restricted to volunteers of European ancestry aged 60 to 73 years at baseline and, therefore, further research is warranted to investigate to what degree these findings generalize to other populations. Seventh, the mean age of participants was 72 years at the end of the follow-up period, which limited the number of incident dementia cases despite the large sample size and long follow-up period. Eighth, incident dementia cases were ascertained through hospital inpatient records and death registry only and some cases of dementia are likely to have been missed. However, research has established good agreement of dementia case ascertainment with primary care records.<sup>35</sup> Ninth, this association study has not been validated in an independently ascertained population.

### Conclusions

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

## ARTICLE INFORMATION

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**Author Contributions:** Drs Llewellyn and Kuźma had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Kuźma and Llewellyn contributed equally.

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**Acquisition, analysis, or interpretation of data:** All authors.

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