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Table S1. 29 SNPs highly associated with AD in genome-wide association studies (GWAS)

SNP	CHR	BP	A1	A2	P	β 系数
rs4575098	1	161155392	A	G	1.9E-10	0.016412
rs6656401	1	207692049	A	G	2.58E-18	0.025014
rs4663105	2	127891427	C	A	1.45E-44	0.031095
rs10933431	2	233981912	G	C	7.62E-10	-0.01544
rs6448453	4	11026028	A	G	1.98E-09	0.014705
rs7657553	4	11723235	A	G	0.044664	0.00484
rs9269853	6	32550322	A	C	3.04E-08	0.013069
rs9381563	6	47432637	C	T	1.99E-10	0.014451
rs1859788	7	99971834	A	G	1.8E-15	-0.0184
rs11763230	7	143108841	T	C	5.37E-09	-0.01577
rs4236673	8	27464929	A	G	1.48E-19	-0.02016
rs11257242	10	11721119	C	G	8.11E-06	-0.01001
rs7935829	11	59942815	G	A	2.7E-15	-0.0176
rs10792832	11	85867875	A	G	4.5E-18	-0.01948
rs11218343	11	121435587	C	T	8.12E-12	-0.03593
rs12590654	14	92938855	A	G	1.32E-10	-0.01483
rs442495	15	59022615	C	T	1.22E-09	-0.01372
rs117618017	15	63569902	T	C	3.44E-08	0.018027
rs59735493	16	31133100	A	G	3.73E-08	-0.01299
rs113260531	17	5138980	A	G	7.91E-10	0.019986
rs28394864	17	47450775	A	G	1.68E-08	0.012302
rs2632516	17	56409089	C	G	7.63E-07	-0.01078
rs8093731	18	29088958	T	C	0.026745	-0.01774
rs76726049	18	56189459	C	T	3.38E-08	0.056797
rs4147929	19	1063443	A	G	4.43E-07	0.014413
rs41289512	19	45351516	G	C	1.5E-278	0.206303
rs76320948	19	46241841	T	C	4.08E-08	0.034933
rs3865444	19	51727962	A	C	5.15E-09	-0.01376
rs6014724	20	54998544	G	A	5.38E-10	-0.02289

Table S2. Candidate features (predictor variables),

Detailed corresponding characterization information can be found at the website (https://biobank.ndph.ox.ac.uk/showcase/search.cgi?tk=2dkZA0VkHxeRYtHzGuFdgeu6jPkTj0Mw459279) for detailed information about the corresponding features

Category	Subcategory	Field ID
Population characteristics (n = 4)	Baseline characteristics (n = 4)	52-0.0, 22189-0.0,31-0.0, 21022-0.0
Cognitive function (n = 4)	Reaction time (n = 4)	20023-0.0,403-0.0,402-0.0,401-0.0
Additional exposure/local environment (n=23)	Residential air pollution (n=17)	24019-0.0,24018-0.0,24017-0.0,24016-0.0,24015-0.0,24014-0.0, 24013-0.0,24012-0.0,24011-0.0,24010-0.0,24009-0.0,24008-0.0, 24007-0.0,24006-0.0,24005-0.0,24004-0.0,24003-0.0
	Residential noise pollution (n=3)	24022-0.0,24021-0.0,24020-0.0,24508-0.0,24507-0.0
	Green areas and near the coast (n=3)	24508-0.0,24507-0.0,24506-0.0
Physical measurements (n = 55)	Body composition measurement via impedance (n = 32)	23130-0.0,23129-0.0,23128-0.0,23127-0.0,23126-0.0,23125-0.0,23124-0.0, 23123-0.0,23122-0.0,23121-0.0,23120-0.0,23119-0.0,23118-0.0 23117-0.0,23116-0.0,23115-0.0,23114-0.0,23113-0.0,23112-0.0,23111-0.0, 23110-0.0,23109-0.0,23108-0.0,23107-0.0,23106-0.0,23105-0.0 23102-0.0,23101-0.0,23100-0.0,23099-0.0,23098-0.0, 21304-0.0
	Body measurements (n = 9)	21002-0.0,21001-0.0,20015-0.0,3077-0.0,51-0.0,50-0.0,49-0.0,48-0.0 21-0.0
	blood pressure (n = 3)	4080-0.0,4079-0.0,102-0.0
	Hand grip strength (n = 2)	47-0.0,46-0.0
	Lung function (n = 9)	3137-0.0,3090-0.0,3089-0.0,3088-0.0,3065-0.0,3064-0.0,3063-0.0,3062-0. 0,23-0.0
Touchscreen questionnaire/ oral interview (n=122)	Family history (n = 6)	20110-0.0,20107-0.0,1883-0.0,1873-0.0,1835-0.0,1797-0.0
	Health and medical history history history (n = 23)	2316-0.0,2335-0.0,2345-0.0,2227-0.0,2207-0.0,2306-0.0,2296-0.0,2188-0. 0,2257-0.0,2247-0.0,6152-0.0,2473-0.0,2463-0.0,2453-0.0,2443-0.0 6179-0.0,6155-0.0,2492-0.0,6149-0.0,6159-0.0, 135-0.0,134-0.0,136-0.0
	Sociodemographics (n = 10)	6142-0.0,6139-0.0,738-0.0,728-0.0,709-0.0,699-0.0,680-0.0,670-0.0 6146-0.0, 21000-0.0
	Lifestyle and environment (n = 74)	1628-0.0,1558-0.0,6144-0.0,1548-0.0,1538-0.0,1518-0.0,1498-0.0,1488-0. 0,1478-0.0,1458-0.0,1448-0.0,1428-0.0,1418-0.0,1408-0.0,1389-0.0,1379- 0.0,1369-0.0,1359-0.0,1349-0.0,1329-0.0,1319-0.0,1309-0.0,1299-0.0,1289 -0.0,2237-0.0,6164-0.0,6162-0.0,1100-0.0,1090-0.0,1080-0.0,1070-0.0,227 7-0.0,2267-0.0,1757-0.0,1747-0.0,1737-0.0,1727-0.0,1717-0.0,1060-0.0,10 50-0.0,1220-0.0,1210-0.0,1190-0.0,1180-0.0,1170-0.0,1160-0.0,20160-0.0,

		1259-0.0,6145-0.0,2100-0.0,2090-0.0,2080-0.0,2070-0.0,2060-0.0,2050-0.0,2040-0.0,2030-0.0,2020-0.0,2010-0.0,2000-0.0,1990-0.0,1980-0.0,1970-0.0,1960-0.0,1950-0.0,1940-0.0,1930-0.0,1920-0.0,6160-0.0,2110-0.0,1031-0.0,20116-0.0,21000-0.0,20117-0.0
	Early life factors (n = 9)	1787-0.0,1777-0.0,1767-0.0,1707-0.0,1697-0.0,1687-0.0,1677-0.0,1647-0.0, 120-0.0
Derived features (variables)）(n=5)	History of high blood pressure (131286-0.0,131294-0.0), history of stroke (42006-0.0,42008-0.0), history of heart attack (42000 -0.0), Polygenic risk score for dementia, APOE (Ɛ4) carrier	

Figure S1. UKB-DementiaPre Tool QR

UKB-DementiaPre Tool

Introduction 1. A concise overview of the utilization of the UKB DementiaPre tool

UKB-DementiaPre Tool's page layout and simple instructions for use: the left page is the input column for participant information data, with a total of 30 items; the upper right Observation interval (years) column is the observation interval of interest, which can be adjusted by sliding buttons; Figure A represents the dynamically predicted individualised dementia risk, and displays the dementia risk's probability values; Figure B represents the predicted dementia risk for the population before 1:5 matching predicted by the UKB-DementiaPre Tool and shows the predicted distribution of dementia risk in the population through a box-and-line plot, which provides a reference to the interquartile position (quartiles) of the predicted probability values of the individualised dementia risk for the individualised dementia risk predicted by Figure A in the population; and the table on the lower right provides a more detailed predicted dementia risk of the population for

different time intervals distributions, providing a more detailed reference to the interquartile position in the population (quartiles) of the predicted individualised dementia risk probability values from the Figure A. In addition to predicting an individual's future dementia risk at different points in time, the UKB-DementiaPre Tool can also predict how much an individual's dementia risk may be reduced by dynamically altering the participant's modifiable risk factors, such as lower peak expiratory flow rate of lung function, diet, lifestyle, and psychiatric factors, to provide an individual suggestion for the early prevention of or intervention in dementia.

Discussion 1. The possible mechanisms by which the features of this dementia prediction model are associated with dementia

Discussion 1.1 Association between age and risk of dementia

Age is the most significant known risk factor for dementia, according to a meta-analysis, the prevalence of dementia doubles with every 10 years of age after 60 years [[1] . It has also been shown that the prevalence and incidence of dementia increases exponentially after the age of 65 years [2]. Furthermore, epidemiological studies in different countries around the world have confirmed that the prevalence and incidence of dementia increases with age[3-5] . Further findings have shown a very high prevalence of amyloid and tau proteins in the brains of patients with dementia, especially in patients aged 80 years and older[6]. This finding deepens our understanding of the relationship between dementia and age, and in particular provides important insights when exploring the underlying mechanisms of dementia. Thus, the present study is in line with previous studies that have shown that increasing age is a very important factor in the increased risk of dementia.

Discussion 1.2 Genetic factors associated with dementia risk

Dementia, especially AD, is the result of a combination of genetic and environmental factors[7]. Dementia, especially AD, is associated with variants in several genes, such as APOE4, NOTCH3, and TREM2[8-10] . Apolipoprotein E (APOE) is a glycoprotein involved in cholesterol homeostasis and lipid metabolism, produced mainly by hepatocytes and astrocytes, and present in plasma and cerebrospinal fluid.APOE has three main forms of alleles: ε4, εe3, and ε2, which are defined by different combinations of two single nucleotide polymorphisms (rs429358 and rs7412)[11] Carriers of the APOE(Ɛ4) allele account for 7% of dementia cases globally and have twice the risk of mild cognitive impairment (MCI) and dementia as non-carriers[12-13] It has also been shown that individuals carrying one APOE (Ɛ4) allele have a 3-4-fold increased risk of developing AD compared to non-carriers, while individuals carrying two ε4 alleles have up to a 15-fold increased risk[14-15] . The results of the present study suggest that APOE(Ɛ4) carriers have a higher risk of dementia in the future, which is consistent with previous studies in the literature. The molecular mechanism by which APOE(Ɛ4) increases the risk of dementia is not well understood[16] , and it has been suggested that it may be related to the Aβ cascade hypothesis, which consists of an increased production and a decreased clearance of Aβ in the brain, increased formation of intracellular tau protein tangles, perturbation of synaptic function, and altered microglial cell responses[17-18] . Considering the key role that APOE (Ɛ4) plays in the development of dementia, therapeutic targeting studies around the APOE genotype are progressively being conducted. Several preliminary studies have been exploring therapeutic avenues based on APOE genotype, particularly approaches targeting APOE (Ɛ4) allele carriers, including immunotherapy, mimetic peptide therapies, structural correctors, and gene therapy[19]. These APOE-targeted therapeutic approaches offer new opportunities for the treatment of dementia, and therapeutic strategies targeting APOE and its receptors may benefit more patients with dementia.

The polygenic risk score (PRS), which combines the effects of many diseases risk-associated genetic variants to form a single score, has been shown to have predictive

value for a wide range of common diseases, including dementia[20-21]. In this study, we selected 29 SNP loci highly associated with AD from a previous GWAS. Each participant's dementia PRS was calculated based on their SNPs and the corresponding weights (β coefficients.) The results of the present study indicated that participants with higher dementia PRS had a higher risk of dementia during follow-up, which is consistent with previous studies[22-23] . In addition, the results of the present study also suggest that this characteristic of dementia PRS also plays an important role in predicting participants' future risk of dementia, which provides a basis for screening individuals for dementia risk in the future.

In addition, the results of the present study showed that those participants whose mothers had AD were at a higher risk of developing dementia, which is in line with previous findings[24-26] . Of all the risk factors for sporadic AD, family history ranks second after age[27] . If a first-degree relative has AD, the risk of developing the disease increases four- to tenfold[28-32] . Maternal inheritance of AD is more common than paternal inheritance of AD[24-25] , and a history of dementia in mothers has been associated with the risk of dementia and AD in their children; therefore, a history of dementia in mothers may be a useful marker for identifying individuals at higher risk of AD[26] , and the dementia prediction model in this study suggests that a history of AD in mothers is an important key characteristic of participants at higher risk of dementia. It has been shown that certain genetic variants associated with AD risk such as genetic variants in mitochondrial DNA and PCDH11X on the X chromosome[33-35] tend to be maternally inherited or imprinted, implying that mothers are more likely to pass on risk factors for AD to the next generation compared to fathers. This difference in inheritance patterns may explain why AD is inherited more frequently and significantly from mothers than from fathers. The research in this study further revealed an important finding: mothers with depression were associated with a high risk of dementia in their children. This association may be related to the genetic characteristics of depression, especially considering that depression, as a complex polygenic genetic disorder, may increase the likelihood of mothers inheriting AD risk to their children[36] . In conclusion, attention and research on genetic background and family health history, especially APOE (Ɛ4)

carriage and maternal health history, are important for early identification and management of dementia risk.

Discussion 1.3 Association of chronic diseases and underlying physical conditions with dementia

There is a strong association between chronic diseases and underlying physical conditions and dementia[37-38] , with cardiovascular risk factors and cardiovascular disease associated with a higher risk of dementia[38]]. In the present study's dementia prediction model, a history of diabetes, a history of stroke, lower right leg adiposity or left leg adiposity, receipt of care/disability/mobility benefits, long-term illness disability or frailty, living in sheltered accommodation and care homes, higher number of self-reported non-cancer illnesses, higher number of falls in the last year, use of prescription medication, lower peak expiratory flow rate for lung function and doctor's diagnosis of other serious medical conditions/disabilities , which are important characteristics in predicting a higher risk of dementia.

Discussion 1.31 Association between chronic diseases and dementia

A history of diabetes is one of the important key characteristics of participants at higher risk of dementia. Many previous prospective studies have reported an association between diabetes and the development of dementia[39-40]. A meta-analysis shows diabetics have a 1.7-fold increased risk of all-cause dementia[39] Another meta-analysis of sex-specific associations between diabetes and the risk of dementia also showed that diabetes was associated with a 60 per cent increased risk of all dementias, regardless of sex[40] The onset of dementia in diabetic patients is gradual, beginning with mild cognitive impairment, then progressing to mild cognitive impairment, and finally to overt dementia[41]. The mechanism of association between diabetes and dementia is unclear, and several possible explanations provide some understanding. Firstly, it may be related to the existence of important and shared pathological features between type 2 diabetes and dementia, which are mainly characterized by metabolic disturbances in the brain, such as insulin resistance, altered glucose uptake and utilization[42-43] . Considering that the

pathophysiological process of dementia may begin many years before the onset of symptoms, early and effective management is essential to prevent the development of dementia in later life in patients with diabetes.

A history of stroke is also one of the important key characteristics of participants at higher risk of dementia. In recent years, stroke has become increasingly prevalent and is the first cause of death in China[44] and the fifth cause of death in the United States[45] . Post-stroke cognitive impairment (PSCI) refers to cognitive deficits that occur 3-6 months after the onset of stroke, with region-specific cognitive impairments mainly caused by the site of stroke injury[46] , e.g., aphasia or memory deficits are clinical manifestations caused by infarcts in the hippocampus, thalamus, and key cortical areas. The results of the present study showed that participants with a history of stroke had a higher risk of dementia, which further suggests that stroke is an important risk factor for dementia risk. At the cellular level, acute stroke-related injury ultimately impairs the function of the neurovascular unit (NVU), and dysregulation of the NVU may accelerate the accumulation of Aβ by reducing clearance and increasing Aβ production[46] . A randomized controlled trial (RCT) showed that the risk of dementia after stroke could be reduced by interventions to control vascular risk factors[47] . People with a history of stroke should be more alert to their risk of dementia and intervene early in vascular risk factors.

Discussion 1.32 Association between poor physical fundamentals and dementia risk

The findings of this study further reveal a significant association between poorer underlying physical condition and increased risk of dementia. Consistent with previous studies, poorer physical condition, multiple health problems are associated with increased risk of dementia[48] . Leg fat ratio and fat mass are important measures of individual fat distribution. Past studies have focused on the association between abdominal fat and dementia, while direct associations between leg fat ratio/fat mass and dementia have been less well studied. A study involving 5169 participants (mean age 76 years, 57.1% female) found that higher amounts of subcutaneous fat in the abdomen and thighs were associated with a reduced risk of dementia in women[49-51] . The possible mechanisms regarding the association of leg fat ratio/fat mass with dementia are not fully understood, with some

studies suggesting a possible association with hormonal regulation, such as estrogen and endogenous estradiol[52-54] . In the present study, using a large population-based study, we found that participants with a lower right leg adiposity ratio or left leg adiposity had a significantly increased risk of developing dementia. This provides a new perspective to further understand the relationship between leg fat and dementia and provides useful information for more in-depth studies in the future.

Participants in receipt of Attendance/Disability/Mobility Allowance or living in sheltered accommodation/care homes represent a group of people in poorer physical condition, who are likely to have a greater combination of underlying conditions. In addition, participants in receipt of Attendance/Disability/Mobility Allowance or living in sheltered accommodation/care homes are also less physically active, and this lack of physical activity leads to a reduction in the functioning of the body's circulatory system, including the cardiovascular system and the circulatory system, which in turn affects the supply of blood to and nutrients from the brain. This may lead to hypoxia and nutritional deficiencies in the brain, accelerating the ageing and death of brain cells, which may increase the risk of dementia[55, 56]. In addition, physical inactivity may also increase the level of inflammation in the body, such as an increased release of pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines, further leading to an overactive inflammatory response[55-56] . A chronic inflammatory state sustained over a long period of time can negatively affect the brain, damaging neurons and inducing the onset of dementia[57] . A chronic inflammatory state sustained over a long period of time can negatively affect the brain, damaging neurons and inducing the onset of dementia[58-59] . Participants in receipt of Care/Disability/Mobility Allowance or living in sheltered accommodation/care homes are likely to represent a less economically privileged group, with lower socio-economic status being recognized as a potential risk factor for the development of dementia[60-62]. Lower socioeconomic status, greater psychosocial stress, poorer lifestyle and risk of reduced cognitive functioning have been associated[63].

In addition, the dementia prediction model in this study found that the number of falls was associated with a higher risk of future dementia. Falls may be a marker of declining health in older adults[64] , and multiple falls may be an important marker for

identifying future cognitive decline in older adults[64-65] . Previous studies have shown that the occurrence of two or more falls is associated with an accelerated rate of cognitive decline as measured by the Measure of Mental Status Examination (MMSE)[66] . The mechanisms by which multiple falls are associated with predicting a higher risk of future dementia may be as follows: firstly, frequent falls may be an indication of cognitive decline and impaired motor coordination, which are strongly associated with the onset of dementia[67-68] . Secondly, it may be related to the fact that falls may lead to behavioral changes; due to fear of future falls, older adults who have experienced multiple falls may become less physically active and become socially isolated, which may indirectly lead to cognitive decline[64, 69] .Therefore, dementia patients with frequent falls should be assessed and intervened in a timely manner, and effective measures should be taken to improve their autonomy and reduce the risk of falling, so as to maintain their physical health and quality of life, and to delay the emergence and progression of dementia symptoms.

Lung function refers to the physiological functional state of the lungs, including aspects of lung capacity, gas exchange, and ventilation. A prospective study based on UK Biobank found that a decline in lung function was associated with an increased risk of all-cause dementia and its related subtypes[70] . In a Rotterdam study, which included approximately 4,765 adults in the Netherlands with a mean age of more than 65 years, FEV1 (Forced expiratory volume in one second), FVC (Forced Vital Capacity, is the maximum volume of air that can be completely exhaled from the lungs of a person after maximum possible The relationship between FVC (Forced Vital Capacity, the maximum volume of air a person can completely exhale from the lungs after the maximum possible exhalation), FEV1/FVC (Forced expiratory volume in one second/forced vital capacity, the ratio of FEV1 to FVC) and all-cause dementia was revealed in a study that found that a reduced FVC was associated with a higher risk of dementia[71] The results of this study suggest that the lower the peak expiratory flow velocity (FEV) of lung function, the higher the risk of dementia. The mechanisms by which decreased lung function is associated with an increased risk of dementia may be as follows: firstly, decreased expiratory function leads to hypoventilation and neurological damage due to cerebral

hypoxia. Secondly, reduced expiratory function produces chronic inflammation and oxidative stress in the brain, which activates microglia aggregation and phosphorylates Tau protein[72] . Therefore, for the elderly and those at high risk of dementia, attention should be paid to maintaining good lung function, performing appropriate lung function training, avoiding bad habits such as smoking, and reducing exposure to environments such as dust that may cause damage to lung function.

Finally, the present study found a strong association between an increased number of self-reported non-cancer diseases, physician diagnosis of other serious conditions/disabilities and increased risk of dementia. Previous studies have shown that having multiple morbidities is associated with an increased risk of dementia, AD and VD, and that the greater the number of morbidities, the higher the hazard ratio (HR) for developing dementia, AD and VD[73] . Although only a few studies have explored the association between multimorbidity and the development of dementia, the findings of these studies support the present study and emphasize the importance of multimorbidity in the development of dementia[74-75].

Overall, this study highlights the importance of early dementia risk assessment and intervention for individuals with poor physical health. Future research should further explore how dementia risk can be reduced by preventing and treating physical health problems and how effective these interventions are in different populations.

Discussion 1.4 Association between economic factors and dementia

The dementia prediction model and model interpretation in this study suggests that economic factors are one of the important features of the model for predicting dementia risk. Previous studies have shown a strong association between the level of economic status and dementia risk[76] . The World Alzheimer's Disease Report 2023 states that as the population ages, it is projected that by 2050 there will be approximately 139 million people with dementia globally, of which approximately two-thirds will live in low- and middle-income countries[77]. Economic factors include individual and household economic status, such as total household income, housing situation and employment

status. One study found that participants with poor health, lack of education and unemployment had a higher risk of dementia, and that poverty level was associated with dementia risk[78]. The results of this study showed that the risk of dementia was higher for participants who had a lower average gross pre-tax household income, were paying rent to rent but not buying a home, were currently unemployed, and were unable to work due to illness or disability. For possible reasons why poor economic factor status is associated with a higher risk of dementia: firstly, economic factors have an impact on educational level and career progression, which are strongly associated with the risk of dementia. Lower levels of education and career progression may lead to less cognitive stimulation and lack of mental activity, increasing the risk of dementia [79-80] . Secondly, economic status has an important impact on dietary habits and lifestyle, which are strongly associated with the development of dementia. Economic hardship may lead to poor dietary patterns and lack of balanced nutritional intake, increasing the risk of dementia [81-82]. Once again, economic factors are related to the accessibility and quality of healthcare, which is crucial for the prevention and treatment of dementia. Economic hardship may lead to insufficient healthcare resources for timely access to specialized dementia prevention, diagnosis and treatment services. Finally, economic hardship may lead to higher levels of psychological stress and depressive symptoms [83-84] , further exacerbating cognitive decline [85-86].

In summary, there is an association between economic factors and dementia. Economic hardship may increase the risk of dementia and influence the course of the disease by affecting educational level and career development, dietary habits and lifestyle, healthcare, and psychological stress. Therefore, society should pay attention to the impact of economic factors on dementia, and take corresponding measures to improve education level, dietary structure, health care services and psychological stress to prevent and manage dementia.

Discussion 1.5 Diet and Lifestyle and Dementia

Interpretation of the dementia prediction model for this study indicated that: participants who consumed the food groups of eggs (or egg-containing), dairy products, wheat, and sugar, or who did not consume sugar or sugar-containing foods/beverages had a lower risk of dementia; there were higher dementia risks associated with longer hours of television per day and with heavy (e.g., carpentry, digging) physical activity; and furthermore, when comparing the change in alcohol intake 10 years ago (more, about the same today, or less now) was not significantly associated with dementia risk. Our findings suggest an association between diet and lifestyle and dementia.

In recent years, more and more epidemiological studies have begun to focus on the relationship between dietary habits and dementia risk. The present study further confirms the importance of a balanced diet and non-consumption of sugary or sugary foods/drinks and for dementia prevention. Specifically, the present study found that participants who did not consume sugary foods/beverages had a significantly lower risk of dementia. This finding is consistent with previous epidemiological studies[21, 87]. In a study of a community-based population of older adults, total sugar intake was found to be significantly associated with a higher risk of AD[87] . Specifically, participants in the group with the highest total sugar intake had a two-fold increased risk of AD compared to participants in the group with the lowest total sugar intake[87] . Another study from the UK Biobank database found that higher intake of sugary and artificially sweetened beverages was associated with a higher risk of dementia[21] . Several mechanisms may explain the relationship between sugary intake and dementia risk. Most sugars are readily converted to glucose in the body and are susceptible to homeostatic regulation by insulin[87]. There is evidence that insulin resistance may play an important role in the development of AD[88-90] . In addition, the way in which glucose is metabolised has been shown to promote inflammation and the formation of reactive oxygen species, both of which are associated with AD, which may be another potentially possible mechanism[91-92]. Based on these findings, promoting a balanced diet and reducing the intake of sugary foods/beverages may be an effective strategy for dementia prevention.

Future studies should further explore the effects of specific dietary interventions and how they can be implemented in different populations.

Today, people spend nearly two-thirds of their leisure time sedentary, with the most common activities including television viewing and computer use [93] . Previous studies have shown that excessive daily television viewing is associated with cognitive decline[94-95]. Television viewing time of 2-3 hours per day was associated with higher all-cause dementia, and television viewing time of greater than or equal to 4 hours per day was associated with higher risk of all-cause dementia, AD, and vascular dementia [96] . Possible explanations for the association of excessive TV viewing time with a higher risk of dementia are as follows. Firstly, TV viewing time is associated with a higher risk of cardiovascular and cardiovascular-metabolic diseases[97] , both of which may result in a crisis of energy metabolism due to insufficient blood supply to the brain as a result of reduced oxygen supply. This hypoxic state may trigger oxidative stress and acidosis, ultimately leading to neuronal degeneration[98-99] . Secondly, television viewing increases sedentary time, leading to reduced muscle activity and energy expenditure[100-101] , further leading to reduced physical activity and cognitive decline [102-103] . Then, excessive television viewing usually means sitting for long periods of time in the evening after eating, which can be harmful to cardiometabolic health[101] , which in turn affects brain health[104] . Finally, prolonged and continuous television viewing causes passive and intense sensory stimulation to the viewer, increasing the cognitive load on the brain and affecting its mood, and therefore may lead to mental and psychological effects[105] . In order to prevent dementia, it is recommended to avoid excessive television viewing, maintain appropriate physical activity and social interactions, have a regular routine, and maintain a balanced diet to maintain physical and mental health, delay cognitive decline, and reduce the risk of dementia.

Physical activity can be classified as mild, moderate and severe according to the degree, including daily activities, physical exercise and occupation-related physical work. One study suggests that approximately 3% of dementia cases can be prevented by appropriate exercise[106] . In addition, a study published in The Lancet that included 7,005 participants showed that intense physical labor increases the risk of dementia or

mild cognitive impairment[107]. This is consistent with the results of the present study, where our results suggest that participants with heavy physical activity, such as carpenters, miners, etc., have a higher risk of dementia. For the possible mechanisms by which heavy physical activity is associated with a higher risk of dementia, there are, firstly, prolonged periods of intense physical activity may lead to chronic inflammation and oxidative stress, and prolonged chronic inflammation and oxidative stress further contribute to the onset and progression of neurodegenerative diseases, including AD[108-109] . Secondly, after heavy or strenuous exercise, it may lead to thrombosis and vascular damage, which in turn may lead to brain hypoxia and nutritional deficiencies that increase the risk of dementia[110] . Therefore, heavy or strenuous exercise should be avoided in the elderly or other people at high risk of dementia, and early screening and detection of dementia risk factors should be performed for early prevention in those who engage in heavy physical activity.

Alcohol intake refers to the amount of alcohol consumed by an individual in a certain pattern or period of time, and is usually categorized as acute alcohol intake and chronic alcohol intake[111] .Previous studies are controversial regarding whether alcohol intake has an impact on cognitive decline or contributes to the development of dementia. The Lancet published a synthesis of 83 prospective cohort studies concluding a safe alcohol intake of 0[112] .Another study showed that moderate alcohol consumption, especially wine, has a protective effect on neurological or cognitive function[113] .The results of this study showed that comparing the changes in alcohol intake 10 years ago (more today, about the same, less now) was not significantly associated with dementia. This suggests that there may be a complex relationship between alcohol intake and dementia or the influence of other factors. Possible reasons for this are, firstly, the complexity of the model of alcohol intake with changes in dose over time, and the fact that moderate amounts of alcohol have a favorable effect on lipid levels by increasing HDL, and affect atherosclerosis and inflammation by decreasing fibrinogen levels and inflammatory markers[114] .Secondly, excess alcohol increases Aβ protein accumulation and Tau protein phosphorylation, which in turn increases neuroinflammation and

neurotoxicity leading to the development of dementia[115]. Therefore, acute or high-dose alcohol intake should be avoided in the elderly or those at high genetic risk.

Discussion 1.5 Association between cognitive function and dementia

Another important feature of the dementia prediction model in this study included participants' reaction time, which is a key indicator for assessing cognitive ability. It has been shown that different measures of reaction time, such as mean reaction time and reaction time variability, have been found to be able to distinguish individuals with dementia from controls without the disease[116-118]. Not only that, but these measurements have also been able to distinguish between different kinds of dementia and mild cognitive impairment (MCI) [119] . Additionally, it has been found that if a person has increased reaction time variability or a longer mean reaction time, they are at an increased risk of developing dementia over the next four years[120] , or are more likely to transition from MCI to AD[121] . These findings emphasize the importance of reaction time measures in the assessment of cognitive function, especially in the early diagnosis of dementia. Another interesting finding from the study was that participants who speed on motorways often or most of the time had a lower risk of dementia. This suggests that these participants may have had faster reflexes and better maneuvering abilities, which somehow protected them from the effects of dementia. However, this finding does not mean that speeding is encouraged, as it increases the risk of road accidents. Research into the relationship between speeding and dementia risk reminds us that cognitive health is closely linked to behavioral patterns in everyday life, and that strengthening participants' manipulation and resilience practice in other ways that are safe could be a potential intervention. While further research is needed to validate these preliminary findings and explore the mechanisms involved, these results provide a valuable perspective for developing new prevention strategies.

Discussion 1.6 Association of psychiatric factors with dementia

Psychiatric factors are strongly associated with dementia, with some studies suggesting that 90% of people with dementia present with psychiatric symptoms such as schizophrenia, mania and depression[122]. A prospective study based on UK Biobank found that depressed mood is a risk factor for dementia, and early treatment of depressed patients to avoid progression to severe can effectively reduce the risk of concurrent dementia[123]. The results of the dementia prediction model in the present study showed that participants who were free of depressed mood and unenthusiastic/uninterested in the last 2 weeks predicted a lower risk of dementia in the future, suggesting that a good and positive psychological state can be a potential measure to reduce the risk of developing dementia in the future. In addition, the present study further used two-way MR to infer a causal association between the absence of low mood and disinterest in the last 2 weeks and the risk of AD, with the lower genetically predicted risk of AD being associated with a lower frequency of 2-week absence of low mood and disinterest, and thus, low mood and disinterest may be one of the early clinical manifestations of dementia. In addition, it has been shown that negative emotional and psychological states can lead to imbalance in neurotransmitter regulation and abnormal transmitter concentrations thus causing depression or dementia[124] . Psychological factors such as low mood and depression can also lead to structural changes in the brain, such as hippocampal volume atrophy[125] , and the overall atrophy of the hippocampus is considered to be one of the specific imaging markers of dementia[126] . Therefore, older adults or others at high risk for dementia should maintain a positive mindset, and individuals who already suffer from mental illnesses such as depression should be intervened early to avoid the development of serious illnesses, as well as screened promptly for the individual's future risk of dementia and strengthened health management.

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