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Parental History of Dementia and the Risk of Dementia: A Cross-Sectional Analysis of a Global Collaborative Study

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Authors' contributions

KWK had full access to all the data in the study and was responsible for the decision to submit for publication.

Study concept and design: KWK, DJO, JBB and DML.

Acquisition of data: JWH, KWK, THK, KPK, BJK, SGK, JLK, SWM, JHP, S-HR, JCY, DYL, DWL, SBL, JJL, JHJ, IS, JN, TRS, AG, RV, ER, NS, MY, MHK, SGR-H, SR, JD, MFDG, KCF, AL, PS, RL-A, KJA, NC, MEM, HB, JNT and NAK.

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Competing interests

All authors declare no competing financial interests.

Supporting information

Supplementary table 1. Separate analyses for every single cohort

Supplementary table 2. Sensitivity analysis leaving one out at a time

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Abstract

Background: Parental history of dementia appears to increase the risk of dementia, but there have been inconsistent results. We aimed to investigate whether the association between parental history of dementia and the risk of dementia are different by dementia subtypes and sex of parent and offspring.

Methods: For this cross-sectional study, we harmonized and pooled data for 17,194 older adults from nine population-based cohorts of eight countries. These studies conducted face-to-face diagnostic interviews, physical and neurological examinations, and neuropsychological assessments to diagnose dementia. We investigated the associations of maternal and paternal history of dementia with the risk of dementia and its subtypes in offspring.

Results: The mean age of the participants was 72.8 ± 7.9 years and 59.2% were female. Parental history of dementia was associated with higher risk of dementia (odds ratio [OR]=1.47, 95% confidence interval [CI]=1.15–1.86) and Alzheimer's disease (AD) (OR=1.72, 95% CI=1.31–2.26), but not with the risk of non-AD. This was largely driven by maternal history of dementia, which was associated with the risk of dementia (OR=1.51, 95% CI=1.15–1.97) and AD (OR=1.80, 95% CI=1.33–2.43) whereas paternal history of dementia was not. These results remained significant when males and females were analyzed separately (OR=2.14, 95% CI=1.28–3.55 in males; OR=1.68, 95% CI=1.16–2.44 for females).

Conclusions: Maternal history of dementia was associated with the risk of dementia and AD in both males and females. Maternal history of dementia may be a useful marker for identifying individuals at higher risk of AD and stratifying the risk for AD in clinical trials.

Keywords

Dementia; Alzheimer's disease; Parental history; Maternal history; Sex

INTRODUCTION

Having parents with dementia can increase the risk of dementia via the inheritance of genetic factors and/or a shared lifestyle or environment. The heritability of dementia

has been estimated to be 43%,[1] with the inheritance of genetic risk factors such as an *apolipoprotein E (APOE) ε4* allele contributing to an increased risk of Alzheimer's disease (AD) in offspring with a parental history of dementia.[2] According to the 2020 report of the Lancet Commission, about half of all dementia cases could be prevented or delayed by modifying 12 risk factors across the lifespan: education (early life), hearing loss, traumatic brain injury, hypertension, alcohol overuse, and obesity (midlife), and smoking, depression, social isolation, physical inactivity, air pollution, and diabetes (late life).[3] Many of these factors tend to be highly shared between parents and their children, including educational attainment,[4] hearing loss,[5] hypertension,[6] alcohol overuse,[7] obesity,[8] and diabetes[9].

Most, but not all, previous studies have found an association between parental history of dementia and the risk of dementia or AD, including a nationwide cross-sectional epidemiological study from China[10] and a large claims-based study.[11] Two case control studies reported the association[12,13] while one did not.[14] Similarly, one prospective cohort study found the association[2] while another did not.[15] In the studies reporting the association, parental history of dementia roughly doubled the risk of dementia or AD.[2,11–13]

Inconsistent results across previous studies might be partly due to the association between parental history of dementia and the risk of dementia being complex. The dementia subtypes of parents were not specified in most previous studies,[2,10,12–15] but the association between parental history of dementia and the risk of dementia may differ by subtype, because the heritability of dementia differs by subtype. For example, AD has a higher heritability than vascular dementia (VaD).[1,16] Most previous studies also did not analyze maternal and paternal histories separately.[10,12–15] However, maternal and paternal histories of dementia may have different associations with the risk of dementia. Maternal inheritance of AD is more common than paternal inheritance of AD,[17,18] and maternal history of dementia, but not paternal history of dementia, is reportedly associated with biomarkers of amyloid deposition[19–21] and neurodegeneration.[21–23] Further, compared to males, females may be more vulnerable to pathologies of neurodegenerative diseases and at greater risk for dementia,[24,25] yet the sex of offspring was not considered in most previous studies.[2,13–15]

To our knowledge, no previous study of the association between parental history of dementia and the risk of dementia has simultaneously considered dementia subtypes, different heritability from mothers and fathers, and sex differences in the risk of dementia. We addressed this in the present cross-sectional study, using the pooled data of nine population-based cohort studies from eight countries. By considering potentially influential factors and having a large heterogenous sample, we intend our findings to more accurately and comprehensively represent the relationship between parental history of dementia and the risk of dementia.

METHODS

Study population

For a cross-sectional analysis, we pooled data from nine member studies of Cohort Studies of Memory in an International Consortium (COSMIC) (Table 1).[26–35] While we used the baseline data of seven studies,[27,29,31–35] for two studies, the Sydney Memory and Ageing

Study (MAS)[28] and Personality And Total Health through life (PATH),[30] we used the most recent follow-up data (6th wave in MAS and 4th wave in PATH). This is because the MAS did not include participants with dementia at baseline and PATH obtained information on parental history of dementia only at wave 4. All participants were randomly sampled from community-dwelling older adults (we excluded institutionalized participants who were also sampled in the Leipzig Longitudinal Study of the Aged).

From an initial total sample of 19,480 participants, we excluded 2,286 participants due to missing data for diagnosis of dementia (N = 519), parental history of dementia (N = 939), educational level (N = 114), hypertension (N = 260), or diabetes mellitus (DM) (N = 454), giving a final sample of 17,194 participants. The included cohorts varied in size from 361 to 6,218 participants.

Measures

All studies diagnosed dementia by face-to-face diagnostic interviews, physical and neurologic examinations, and neuropsychological assessments[26] according to Diagnostic and Statistical Manual of Mental Disorders criteria, with eight using the Fourth edition (DSM-IV)[36] and one[33] using the Third Edition, Revised (DSM-III-R).[37] All studies also provided data on dementia subtypes. Six studies[29,31–35] diagnosed AD according to the National Institute of Neurological and Communicative Diseases and Stroke/ Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[38] two studies[27,30] according to the DSM-IV criteria,[36] and one study[28] according to DSM-5 criteria.[39] Five studies[29,31–33,35] diagnosed VaD according to the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et 1'Enseignement en Neurosciences (NINDS-AIREN) criteria,[40] two studies[27,30] according to the DSM-IV criteria,[36] one study[28] according to DSM-5 criteria,[39] and one study[34] according to the Hachinski ischemic scale.[41] We classified cases with mixed dementia, both AD and VaD, as AD.

All studies provided data on parental (paternal and maternal) history of dementia, age, sex, educational level, presence of hypertension and DM (all harmonized when necessary). All studies but the Zaragoza Dementia Depression Project (ZARADEMP) determined *APOE* genotype. Across the other eight studies, 9,397 (75%) participants had data on *APOE* genotype. Hypertension was defined by self-report of medical history, current medication and/or measured blood pressure of ≥ 140/90. DM was defined by self-report of medical history, current medication, and/or fasting blood glucose ≥126mg/dL or >7mmol/L.

Analysis

We compared continuous variables between groups using Student's t tests and categorical variables using chi square tests. We examined the associations of parental, maternal and paternal histories of dementia with the risk of all-cause dementia using binary logistic regression analysis, and with the risks of AD, VaD and other dementia (OD) using multinomial logistic regression analysis. In both analyses, we adjusted for age, educational level, hypertension, DM and cohort as covariates. In the subgroup with *APOE* genotype data we repeated the analyses with additional adjustment for *APOE* genotype. We examined the

interaction between maternal/paternal history of dementia and sex of the participants using multinomial logistic regression analysis computing maternal/paternal history of dementia, sex of the participants, and their interaction as independent variables, diagnosis (normal, all-cause dementia, AD, VaD, and OD) as a dependent variable, and age, educational level, hypertension, DM and cohort as covariates. We also estimated the risk of AD associated with maternal/paternal history of dementia in male and female participants separately. To investigate heterogeneity across the cohorts, we used the restricted maximum likelihood method.

As sensitivity analyses, we conducted leave-one-out analyses for each outcome by omitting each study in turn from the pooled dataset to determine if any single study unduly influenced the results. Considering differences among cohorts in the prevalence of parental history of dementia, we also conducted the analysis by omitting studies with a prevalence of parental history lower than the mean prevalence across all participants (10.2%). To examine whether the results were affected by ethnicity, we performed logistic regression analysis computing maternal/paternal history of dementia, ethnicity, and their interaction as independent variables, dementia diagnosis as a dependent variable, and age, educational level, hypertension, DM and cohort as covariates.

The KLOSCAD team harmonized and pooled the datasets, and performed the analyses using the Statistical Package for Social Sciences, v20 (SPSS Inc., Chicago, IL).

Ethics approval and consent to participate

This study conformed to the provisions of the Declaration of Helsinki and was approved by the University of New South Wales Human Research Ethics Committee (Ref: # HC12446). All nine studies that were involved in this research had previously received approval from their own institutional review boards to ensure ethical standards were met, and all participants willingly provided informed consent.

RESULTS

The mean age of the 17,194 included participants (7,022 male and 10,172 female) was 72.8 ± 7.9 years old. The proportion of participants for which one parent had dementia was 10.2% (N = 1753), and for which both parents had dementia was 0.5% (N = 84). Maternal history of dementia was more common than paternal history of dementia in all cohorts (Table 1). Participants with a parental history of dementia were younger, more educated and less likely to have hypertension, though more likely to have an *APOE ε4* allele than those without a parental history of dementia. These results were similar when paternal and maternal history of dementia were analyzed separately (Table 2).

As summarized in Table 3, parental history of dementia was associated with a 1.5 times higher risk of dementia (odds ratio [OR] = 1.47, 95% confidence interval [CI] = 1.15 – 1.86, p = 0.002). When analyzed with the risks of AD, VaD and OD separately, parental history of dementia was associated with the risk of AD (OR = 1.72, 95% CI = 1.31 – 2.26, p < 0.001), but not with the risk of VaD (OR = 0.99, 95% CI 0.54 – 1.81, p = 0.963) or OD (OR = 0.92, 95% CI = 0.44 – 1.93, p = 0.822). The association between parental history of dementia and

the risk of AD remained significant (OR = 1.54, 95% CI = 1.06 – 2.23, p = 0.023) in the subgroup analysis where we further adjusted for the presence of an *APOE ε4* allele.

Table 4 shows results for separate analyses of paternal and maternal history of dementia. Maternal, but not paternal, history of dementia was associated with higher risks of all-cause dementia (OR = 1.51, 95% CI = 1.15 – 1.97, p = 0.003) and AD (OR = 1.80, 95% CI = 1.33 – 2.43, p < 0.001). With further adjustment for the presence of *APOE ε4* allele in the subgroup of participants with *APOE* genotype data, maternal history of dementia remained associated with the risk of AD (OR = 1.64, 95% CI = 1.10 – 2.44, p = 0.014), but not with the risk of all-cause dementia (OR = 1.19, 95% CI = 0.82 – 1.72, p = 0.361). The association between maternal history of dementia and risk of AD was found for both male (OR = 2.14, 95% CI = 1.28 – 3.55, p = 0.003) and female (OR =1.68, 95% CI = 1.16 – 2.44, p = 0.006) participants (interaction not significant, p = 0.217). Paternal history of dementia was not associated with the risk of AD in either male (OR = 0.94, 95% CI = 0.37 – 2.40, p = 0.894) or female (OR =1.71, 95% CI = 0.94 – 3.09, p = 0.077) participants (interaction not significant, p = 0.458).

Supplementary table 1 shows the distribution of ORs and 95% CIs for each cohort. For the association between maternal history of dementia and the risk of AD, the restricted maximum likelihood method found no significant heterogeneity between studies (I^2 = 0.0%; H = 0.943; Tau^2 = 0; Cochran's Q = 6.94; P = 0.543). Sensitivity analyses omitting one study at a time produced no statistically significant changes in the above results (Supplementary table 2). After excluding studies with a prevalence of parental history lower than 10.2% (Invece.Ab, KLOSCAD, and ZARADEMP), the association of maternal history of dementia with AD risk remained significant (OR = 2.16, 95% CI = 1.52 – 3.07, p < 0.001). In another sensitivity analysis adjusting for ethnicity, the association between maternal history of dementia and risk of AD remained significant (OR = 1.97, 95% CI = 1.36 – 2.87, p < 0.001) (interaction not significant, p = 0.406).

DISCUSSION

With cross-sectional analysis of data for over 17,000 community-dwelling older adults from nine population-based cohort studies, we found that maternal history of dementia was associated with an increased risk of AD in both males and females. These results remained significant after adjusting for the presence of an *APOE ε4* allele.

Previous studies into the association between parental history of dementia and the risk of dementia or AD have produced mixed results. The association between parental history of dementia and the risk of dementia and AD were reported in a case-control study (Relative risk [RR] for AD = 2.3, 95% CI = 1.8 – 3.1),[12] a prospective cohort study (Hazard ratio [HR] for dementia = 1.67, 95% CI = 1.12 – 2.48 and HR for AD = 2.01, 95% CI = 1.27 – 3.18),[2] and a large claim-based study (RR for AD = 1.73, 95% CI = 1.59 – 1.87).[11] The excess risks of dementia and AD with parental history of dementia in the current study are comparable to estimates from previous studies reporting significant association. However, there was no significant association between parental history of dementia and the risks of dementia and AD in a case-control study from Washington[14] and in a prospective study from

Stockholm.[15] Both studies that failed to find a significant association may have been limited by small sample sizes and small number of AD cases.

The increase in the risk of dementia associated with parental history of dementia we found was largely due to an increase in the risk of AD. Parental history of dementia increased the risk of AD by around 1.7 times, but there was no association with the risk of non-AD, including VaD. In terms of heritability, this could reflect the likelihood of parental dementia being AD rather than another subtype.[42,43] In addition, the heritability of AD is reportedly higher than the heritability of VaD, which is the most prevalent dementia subtype other than AD.[1,16,42,43]

We found that maternal, but not paternal, history of dementia increased the risk of AD, which is in line with previous family studies.[17,18,44–46] Among individuals with AD and a family history of dementia, the ratio of mothers to fathers with dementia was previously found to be from 1.8 to 3.8.[17,44–46] The ratio of 3.2 in the current study is consistent with this. However, epidemiological studies have found that paternal history of dementia also increased the risk of AD. A study of 2.7 million individuals on the Utah Population Database and with linked death certificates reported that both maternal and paternal histories of dementia were associated with the risk of AD.[11] Despite its large sample size, that claim-based study may have missed many individuals with AD when not indicated in the death certificate and potential confounding factors were not controlled for. Another study from a population-based cohort also found that not only maternal but also paternal history of dementia increased the risk of AD.[2] However, the results have limited generalizability given the study population was from a single district of one city, was of a relatively small sample size, comprised a single ethnicity, and had an unusually high frequency of parental history of dementia (19.6%). By analyzing the pooled data of heterogenous population-based cohorts, the current study may provide more reliable evidence for the heritability of AD being different by the sex of parents.

There are possible explanations for why maternal transmission of AD seems to be more frequent and stronger than paternal transmission of AD. Compared to cognitively normal individuals with a paternal history of AD, cognitively normal individuals with a maternal history of dementia or AD are reported to show higher and more widespread 11C-Pittsburgh Compound B retention,[19] lower amyloid beta 42/40 ratio,[20,21] higher cerebrospinal fluid tau/Aβ ratio,[21] lower gray matter volume in the parietal cortex[22] and reduced glucose metabolism on FDG-PET.[23] Further, some genetic variants associated with the risk of AD, such as genetic variation in mitochondrial DNA,[47] PCDH11X on X chromosome,[48] and imprinted genes[49] are maternally inherited or imprinted, and mothers are more likely than fathers to share AD risk factors with their children.[5,50,51]

Our results indicate that the risk of AD associated with maternal history of dementia was comparable between sons and daughters. Previous studies have shown that the association between history of dementia in parents[2] or first degree relatives[11] and risk of dementia was comparable for males and females. There is evidence suggesting that among individuals with the *APOE ε3/ε4* genotype, females are 1.5 times more likely than males to develop AD,[52]

and it is thus imporant that we controlled for *APOE* genotype when doing separate analyses for males and females. Not all previous strudies have done this.

In the current study, the prevalence of parental history of dementia was 10.2% across all participants, though ranged widely across cohorts from 6.4% in ZARADEMP to 25.8% in H70. This large difference in the parental history of dementia could be attributed to information bias. Recall bias is particularly important to consider because parental history of dementia were self-reported by participants and/or their legal guardians, the accuracy of which has been reported to be 84%.[53] Further, the participants that indicated 'no parental history of dementia' might have had parents with undiagnosed dementia, given that more than 60% of people with dementia are undiagnosed in the community.[54] Selection bias should also be considered because 11.7% of participants were excluded due to missing data. Even so, the association between parental history of dementia and the risk of AD showed a similar tendency in each cohort, and remained significant with sensitivity analysis in which single studies were omitted one by one or studies with lower-than-average prevalence of parental history of dementia were excluded. Our sensitivity analyses supported the linkage of dementia among parents with risk in offspring. There is a need for a further prospective cohort study, based on representative samples, that accurately ascertains dementia cases in both parents and offspring using precise diagnostic information.

Our study has several limitations. First, the ages of onset or diagnosis of dementia and the longevity of parents were not available in the current study. Therefore, sex differences in longevity might have influenced the differential association of dementia risk with the maternal and paternal history of dementia. Second, we did not have data on the dementia subtype of parents. Third, potential differences in health seeking behaviors and aknowledgement of cognitive problems between male and female might have differentially influenced the chance to be diagnosed with dementia between mothers and fathers. Fourth, potential confounding variables other than sex, education, hypertension, DM, and *APOE* genotype could not be controlled because they were evaluated only in some studies. Fifth, moderate to severe offspring dementia might have been underrepresented because all participants were community-dwelling.

To conclude, the maternal history of dementia increases the risk of AD in both male and female. Maternal history of dementia may be a useful marker for identifying individuals at higher risk of AD and stratifying participants in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Availability of data and materials

KWK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1.

Contributing cohorts

	H70	HELIAD	Invece.Ab	KLOSCAD	LEILA 75+	MAS	MMAP	PATH	ZARADEMP	All
Reference	Thorvaldsson et al.[33] [2017]	Dardiotis et al.[32] [2014]	Guaita et al.[31] [2013]	Han et al.[35] [2018]	Riedel-Heller et al.[27] [2001]	Sachdev et al.[28] [2010]	Dominguez et al.[34] [2018]	Anstey et al.[30] [2012]	Lobo et al.[29] [2011]	-
Schedule										
Start	2000	2009	2009	2010	1997	2005	2011	2001	1994	-
End	Ongoing	Ongoing	2015	2020	2014	Ongoing	Ongoing	2021	Ongoing	-
Interval *	2–4 years	3 years	2 years	2 years	5 years	2 years	5 years	4 years	1–5 years	-
Location	Gothenburg, Sweden	Larissa and Marousi, Greece	Milan, Italy	Nationwide, South Korea	Leipzig, Germany	Sydney, Australia	Marikina, Philippines	Canberra and Queanbeyan, Australia	Zaragoza, Spain	-
Participants										
Ethnicity	White	White	White	Asian	White	White	Asian	White	White	-
Age †	73.9 ± 4.9	73.1 ± 5.7	72.2 ± 1.3	70.2 ± 6.9	81.5 ± 5.0	86.9 ± 4.2	69.6 ± 6.6	75.2 ± 1.6	73.5 ± 9.7	72.8 ± 7.9
Numbers										
All	1018	2062	1321	6818	1265	465	1367	361	4803	19480
Included	796	1961	1304	6218	814	406	672	354	4669	17194
Dementia	20	90	39	254	85	91	57	26	199	861
AD	10	70	13	194	50	65	49	23	131	605
VaD	4	7	13	36	27	13	6	1	49	156
OD	6	13	13	24	8	13	2	2	19	100
Family history §										
Parental	205(25.8)	215(11.0)	103(7.9)	582(9.4)	96(11.8)	63(15.5)	121(18.0)	67(18.9)	301(6.4)	1753(10.2)
Maternal	144(18.1)	159(8.1)	90(6.9)	481(7.7)	64(7.9)	44(10.8)	106(15.8)	51(14.4)	199(4.3)	1338(7.8)
Paternal	80(10.1)	61(3.1)	14(1.1)	127(2.0)	34(4.2)	19(4.7)	35(5.2)	19(5.4)	111(2.4)	499(2.9)
Both	19(2.4)	4(0.2)	1(0.1)	26(0.4)	2(0.2)	0(0.0)	20(3.0)	3(0.8)	9(0.2)	84(0.5)

H70, Gothenburg H70 Birth Cohort Studies; HELIAD, Hellenic Longitudinal Investigation of Aging and Diet; Invece.Ab, Invecchiamento Cerebrale in Abbiategrasso; KLOSCAD, Korean Longitudinal Study on Cognitive Aging and Dementia; LEILA75+, Leipzig Longitudinal Study of the Aged; MAS, The Sydney Memory and Ageing Study; MMAP, Marikina Memory and Aging Project; PATH, Personality And Total Health through life; ZARADEMP, Zaragoza Dementia Depression Project; AD, Alzheimer's disease; VaD, vascular dementia; OD, other types of dementia

* follow-up interval

† age (years) at the baseline assessment presented as mean ± standard deviation

§ presented as numbers of participants (percentage)

Table 2.

Demographic and clinical characteristics of the participants

Characteristics	Parental history			Paternal history			Maternal history		
	No (N = 15441)	Yes (N = 1753)	p*	No (N = 16695)	Yes (N = 499)	p*	No (N = 15856)	Yes (N = 1338)	p*
Age, years	72.8 ± 7.9	71.4 ± 7.7	<0.001	72.8 ± 7.9	71.4 ± 7.7	<0.001	72.9 ± 7.9	70.8 ± 7.3	<0.001
Female, N(%)	9110(59.0)	1062(60.6)	0.184	9883(59.2)	293(58.7)	0.838	9355(59.0)	818(61.1)	0.126
Educational level, years	8.1 ± 4.7	9.7 ± 4.7	<0.001	8.1 ± 4.7	9.7 ± 4.7	<0.001	8.0 ± 4.7	9.7 ± 4.5	<0.001
Hypertension, N(%)	8956(58.0)	919(52.4)	<0.001	9616(57.6)	259(51.9)	0.011	9181(57.9)	698(52.2)	<0.001
Diabetes mellitus, N(%)	2671(17.3)	282(16.1)	0.212	2872(17.2)	81(16.2)	0.557	2743(17.3)	215(16.1)	0.282
Apolipoprotein E e4 (+)*, N(%)	3289(21.3)	498(28.4)	<0.001	3673(22.0)	134(26.8)	0.056	3393(21.4)	385(28.8)	< 0.001

Age and educational level are presented as mean ± standard deviation.

*Student t test for continuous variables and chi square test for categorical variables *9397 particpants (8296 without parental history and 1101 with parental history) had data on *apolipoprotein E* genotype

Table 3.

The risk of dementia associated with parental history of dementia

	Number of participants				Risk of dementia*			Risk of AD†			Risk of VaD†			Risk of OD†		
	Control	**Dementia**	**AD**	**VaD**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
Model 1‡																
None	14674	767	531	144	1.00			1.00			1.00			1.00		
Parental	1659	94	74	12	**1.47**	**1.15–1.86**	**0.002**	**1.72**	**1.31–2.26**	**<0.001**	0.99	0.54–1.81	0.963	0.92	0.44–1.93	0.822
Model 2§																
None	7938	358	245	63	1.00			1.00			1.00			1.00		
Parental	1055	46	41	2	1.13	0.80–1.59	0.482	**1.54**	**1.06–2.23**	**0.023**	0.27	0.07–1.13	0.073	0.50	0.15–1.62	0.245

OR, odds ratio; CI, confidence intervals; AD, Alzheimer's disease; VaD, Vascular dementia, OD; Other dementia

*binary logistic regression analyses

†multinomial logistic regression analyses

‡adjusted for age, educational level, hypertension, diabetes mellitus and cohort as covariates

§adjusted for age, educational level, hypertension, diabetes mellitus, cohort and the presence of *APOE ε4* allele as covariates

Table 4.

The risk of dementia associated with paternal and maternal history of dementia

	Number of participants				Risk of dementia*			Risk of AD†			Risk of VaD†			Risk of OD†		
	Control	**Dementia**	**AD**	**VaD**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
APOE ε4 unadjusted‡																
Paternal																
No	15860	835	586	152	1.00			1.00			1.00			1.00		
Yes	473	26	19	4	1.35	0.88–2.07	0.173	1.45	0.88–2.38	0.144	1.07	0.39–2.95	0.898	1.22	0.38–3.95	0.739
Maternal																
No	15069	787	545	147	1.00			1.00			1.00			1.00		
Yes	1264	74	60	9	**1.51**	**1.15–1.97**	**0.003**	**1.80**	**1.33–2.43**	**<0.001**	1.02	0.51–2.03	0.966	0.76	0.31–1.90	0.559
APOE ε4 adjusted§																
Paternal																
No	8721	392	276	65	1.00			1.00			-			1.00		
Yes	272	12	10	0	1.20	0.64–2.25	0.561	1.50	0.75–2.98	0.252	-	-	-	1.38	0.32–5.94	0.663
Maternal																
No	8157	366	251	63	1.00			1.00			1.00			1.00		
Yes	836	38	35	2	1.19	0.82–1.72	0.361	**1.64**	**1.10–2.44**	**0.014**	0.37	0.09–1.54	0.171	0.22	0.03–1.57	0.130

OR, odds ratio; CI, confidence intervals; AD, Alzheimer's disease; VaD, Vascular dementia; OD, Other dementia

The risk of paternal history of dementia on the risk of VaD could not be estimated because there was no vascular dementia patients with parental history of dementia

*binary logistic regression analyses

†multinomial logistic regression analyses

‡adjusted for age, educational level, hypertension, diabetes mellitus and cohort as covariates

§adjusted for age, educational level, hypertension, diabetes mellitus, cohort and the presence of *APOE ε4* allele as covariates