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

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

[1] Department of Epidemiology, Erasmus MC– University Medical Center Rotterdam, Rotterdam, the Netherlands

[2] Department of Cardiology, Erasmus MC – University Medical Center Rotterdam, Rotterdam, the Netherlands

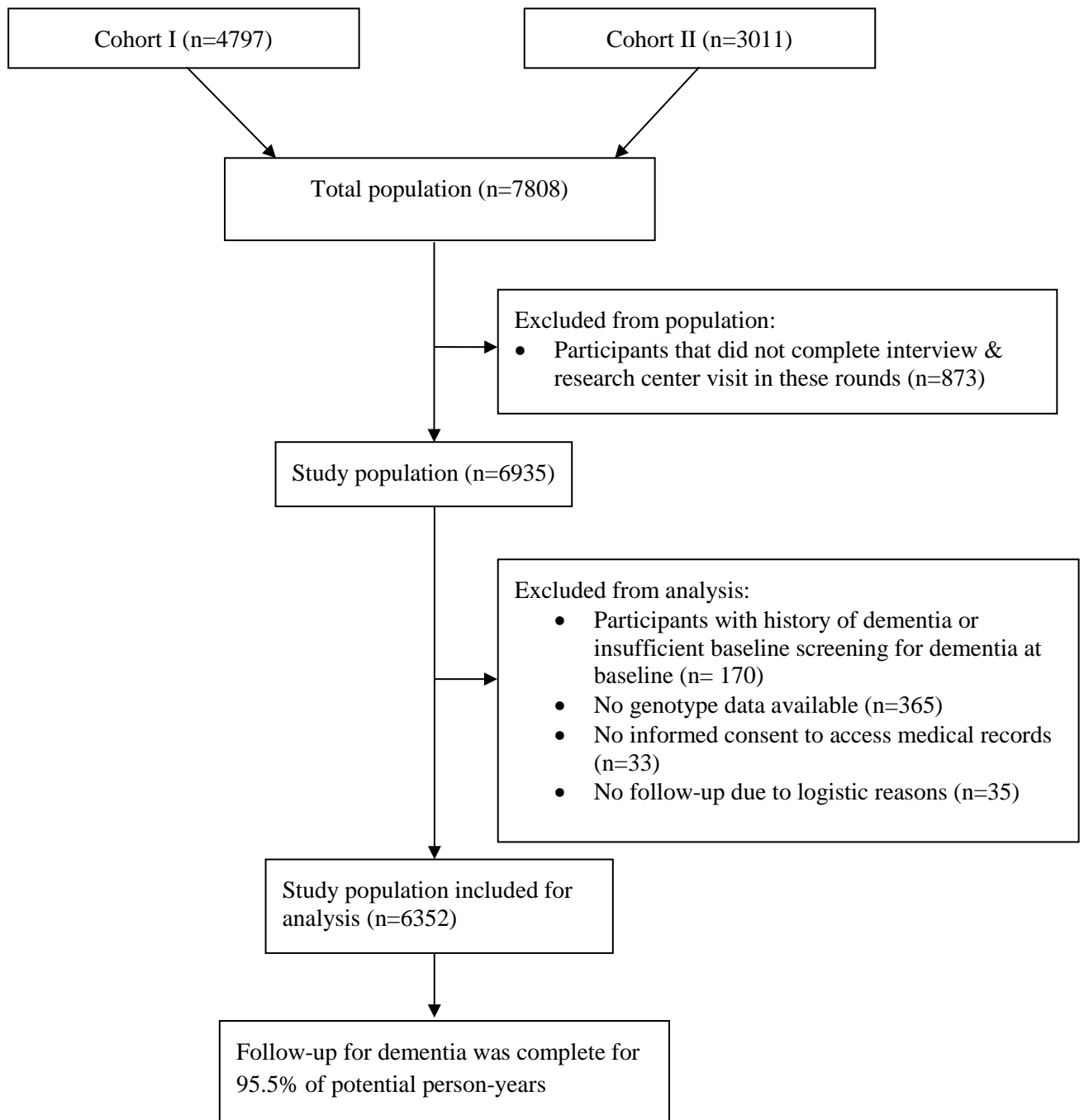[3] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States

[4] Department of Neurology, Erasmus MC– University Medical Center Rotterdam, Rotterdam, the Netherlands

Appendix A. Supplementary figure

Figure 1. Flow-chart of study population

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┌──────────────────────┐              ┌──────────────────────┐
│  Cohort I (n=4797)    │              │  Cohort II (n=3011)  │
└──────────────────────┘              └──────────────────────┘
            ↘                              ↙
            ┌──────────────────────────────────┐
            │  Total population (n=7808)        │
            └──────────────────────────────────┘
                            │
                            │──────────────→ ┌─────────────────────────────────────────────┐
                            │                │ Excluded from population:                   │
                            │                │ • Participants that did not complete         │
                            │                │   interview & research center visit in       │
                            │                │   these rounds (n=873)                       │
                            │                └─────────────────────────────────────────────┘
                            ↓
            ┌──────────────────────────────────┐
            │  Study population (n=6935)        │
            └──────────────────────────────────┘
                            │
                            │──────────────→ ┌─────────────────────────────────────────────┐
                            │                │ Excluded from analysis:                     │
                            │                │  • Participants with history of dementia or  │
                            │                │    insufficient baseline screening for       │
                            │                │    dementia at baseline (n= 170)             │
                            │                │  • No genotype data available (n=365)        │
                            │                │  • No informed consent to access medical     │
                            │                │    records (n=33)                            │
                            │                │  • No follow-up due to logistic reasons      │
                            │                │    (n=35)                                    │
                            │                └─────────────────────────────────────────────┘
                            ↓
            ┌──────────────────────────────────┐
            │  Study population included for    │
            │  analysis (n=6352)                │
            └──────────────────────────────────┘
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            ┌──────────────────────────────────┐
            │  Follow-up for dementia was       │
            │  complete for 95.5% of potential  │
            │  person-years                     │
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Table 1. Genetic variants included in the polygenic risk score

Chr	BP	SNP	Gene	Risk allele	Locus discovered in	Effect size	Minor Allele	Maf_RS1	R^2-RS1	R^2-RS2
1	207802552	rs4844610	CR1	A	Lambert et al. (2009)	0.157003749	A	0.19039	0.9968	0.99498
2	127892810	rs6733839	BIN1	T	Seshadri et al.	0.182321557	T	0.39584	0.95965	0.91998
2	233981912	rs10933431	INPP5D	C	Lambert et al.	0.094310679	G	0.21024	0.93279	0.92668
5	88223420	rs190982	MEF2C	A	Lambert et al. (2013)	0.061875404	G	0.395	0.97929	0.93602
6	41129252	rs75932628	TREM2	T	Guerreiro et al. , Jonsson et al.	0.732367894	T	0.00197	0.7976	0.77763
6	47431284	rs9473117	CD2AP	C	Hollingworth et al. , Naj et al.	0.086177696	C	0.27668	0.99424	0.99517
6	41129207	rs143332484	TREM2	T	Sims et al. , (2017)	0.457424847	T	0.01288	0.83663	0.8099
7	100091795	rs12539172	ZCWPW1	C	Lambert et al., Kunkle et al.	0.083381609	T	0.34739	0.99958	0.99947
7	143099133	rs10808026	EPHA1	C	Hollingworth et al. , Naj et al.	0.105360516	A	0.20154	0.98093	0.98031
7	37844263	rs4723711	NME8	A	Lambert et al. (2013)	0.061875404	T	0.35445	0.99933	0.99924
8	27219987	rs73223431	PTK2B	T	Lambert et al. (2013)	0.09531018	T	0.38498	0.99562	0.99678
8	27467686	rs9331896	CLU	T	Harold et al. , Lambert et al. (2009)	0.127833372	C	0.39809	0.90325	0.97633
11	47380340	rs3740688	CELF1	T	Lambert et al. (2013)	0.083381609	G	0.4464	0.98617	0.98504
11	59936926	rs7933202	MS4A2	A	Hollingworth et al. , Naj et al.	0.116533816	C	0.40726	0.99544	0.99719
11	85868640	rs3851179	PICALM	C	Harold et al.	0.127833372	T	0.37041	0.9992	0.99951
11	121435587	rs11218343	SORL1	T	Lambert et al. (2013)	0.223143551	C	0.04651	0.9979	0.99592
14	53391680	rs17125924	FERMT2	G	Lambert et al. (2013)	0.131028262	G	0.09948	0.99862	0.99842
14	92932828	rs12881735	SLC24A4	T	Lambert et al. (2013)	0.083381609	C	0.24057	0.99526	0.99591
15	59045774	rs593742	ADAM10	A	Kunkle et al. (2019)	0.072570693	G	0.33247	0.99626	0.99625
16	19808163	rs7185636	IQCK	T	Kunkle et al. (2019)	0.083381609	C	0.17569	0.98562	0.98756
16	79355857	rs62039712	WWOX	A	Kunkle et al. (2019)	0.148420005	A	0.12707	0.77987	0.80096
16	81942028	rs72824905	PLCG2	C	Sims et al. , (2017)	0.431782416	C	0.01013	0.94589	0.94491
17	61538148	rs138190086	ACE	A	Kunkle et al. (2019)	0.262364264	A	0.01703	0.83116	0.86548
17	47297297	rs616338	ABI3	T	Sims et al. , (2017)	0.350656872	T	0.01137	0.64079	0.62751
19	1056492	rs3752246	ABCA7	G	Hollingworth et al. , Naj et al.	0.139761942	G	0.16336	0.91902	0.93084
20	54997568	rs6024870	CASS4	G	Lambert et al. (2013)	0.127833372	A	0.0815	0.9842	0.98621
21	28156856	rs2830500	ADAMTS1	C	Kunkle et al. (2019)	0.072570693	A	0.30571	0.97586	0.97907

Ordered by chromosome number. Effect estimates taken from Kunkle et al.[1] and Sims et al.[2] (TREM2- rs143332484, PLCG2 and ABI3) Additional references: Harold et al.[3], Seshadri et al.[4], Hollingworth et al.[5], Naj et al.[6], Lambert et al. (2009,2013)[7,8], Jonsson et al.[9], and Ruiz et al.[10] Minor allele Frequency (Maf) of Rotterdam Study (RS) 1 is shown and is representative of the MAF in RS2. R^2= imputation quality. RS1= initial Rotterdam Study cohort and RS2=first extension Rotterdam Study. Rotterdam Study cohorts were imputed separately. Gene names are ncbi gene names assigned to the loci in the corresponding references

Table 2. Absolute 15-year anticipated risk of dementia according to modifiable risk factor profiles, across different levels of genetically determined risk based on *APOE* carrier status

		N/n	Low genetic risk Mean (95% CI)	N/n	Intermediate genetic risk Mean (95% CI)	N/n	High genetic risk Mean (95% CI)
Overall	Overall	887/85	15.8% (4.6;32.0)	3718/456	16.1% (10.0;19.2)	1747/374	18.6% (12.8;23.8)
Modifiable risk factor profile	Favorable	568/44	12.6% (4.5;26.8)	2453/253	13.5% (8.9;15.6)	1132/241	18.2% (12.7;22.2)
	Intermediate	224/23	16.7% (8.0;36.5)	884/139	20.6% (12.6;22.1)	443/97	19.2% (12.6;21.7)
	Unfavorable	95/18	32.1% (0.0;59.9)	381/64	22.0% (8.3;39.2)	172/36	19.5% (2.5;27.3)

Based on age, sex, education, and modifiable risk factor profile. Confidence intervals computed based on 1000 bootstrap samples. Since baseline characteristics of participants across strata of genetic risk are not identical, anticipated absolute risks may vary beyond the contribution of genetic and modifiable risk factors. Given that these estimations also take into account the contribution of other risk factors for dementia risk, namely age, sex and educational level, predicted risks are not directly comparable across genetic and modifiable risk strata.

Abbreviations: N=number of people at risk, n=number of cases.

Table 3. Risk of incident dementia stratified by modifiable risk factor profiles and genetic risk, separately for participants below and above the median age (68.2 years)

Genetic risk		Low		Intermediate		High	
		N/n	HR (95% CI)	N/n	HR (95% CI)	N/n	HR (95% CI)
	Favorable	311/7	Ref.	1421/110	Ref.	641/79	Ref.
<68.2 years	Intermediate	84/2	1.21 (0.24;6.19)	371/19	1.71 (1.00;2.93)	207/27	1.23 (0.80;1.92)
	Unfavorable	33/3	7.50 (1.73;32.4)	133/10	2.69 (1.33;5.44)	64/6	0.96 (0.42;2.23)
	Favorable	257/37	Ref.	1319/46	Ref.	491/162	Ref.
≥68.2 years	Intermediate	140/21	1.14 (0.96;1.36)	513/120	1.26 (1.00;1.60)	236/70	0.97 (0.73;1.30)
	Unfavorable	62/15	1.31 (1.04;1.63)	248/54	1.33 (0.97;1.82)	118/30	1.05 (0.70;1.57)

Adjusted for: age, sex and education

Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval.

Table 4. Risk of incident dementia stratified by modifiable risk factor profiles and genetic risk, separately for participants below and above age of 70 years

Genetic risk		Low		Intermediate		High	
		N/n	HR (95% CI)	N/n	HR (95% CI)	N/n	HR (95% CI)
	Favorable	351/10	Ref.	1515/65	Ref.	716/90	Ref.
<70.0 years	Intermediate	98/3	1.29 (0.35;4.81)	423/25	1.68 (1.06;2.68)	239/3	1.19 (0.79;1.78)
	Unfavorable	39/4	3.93 (1.19;12.94)	157/10	1.80 (0.92;3.53)	73/11	1.65 (0.87;3.13)
	Favorable	217/34	Ref.	938/188	Ref.	416/151	Ref.
≥70.0 years	Intermediate	126/20	1.14 (0.63;2.05)	462/114	1.25 (0.98;1.59)	204/64	0.95 (0.70;1.29)
	Unfavorable	56/14	2.18 (1.12;4.24)	224/54	1.38 (1.00;1.89)	99/25	0.85 (0.55;1.31)

Adjusted for: age, sex and education

Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval.

Table 5. Risk of incident dementia stratified by modifiable risk factor profiles and genetic risk, separately for men and women

Genetic risk		Low		Intermediate		High	
		N/n	HR (95% CI)	N/n	HR (95% CI)	N/n	HR (95% CI)
Men	Favorable	252/15	Ref.	1185/110	Ref.	557/108	Ref.
	Intermediate	74/3	0.88 (0.25;3.09)	350/41	1.39 (0.96;2.00)	175/22	0.84 (0.52;1.33)
	Unfavorable	32/5	3.72 (1.24;11.1)	109/8	1.04 (0.50;2.17)	45/5	0.67 (0.27;1.68)
Women	Favorable	316/29	Ref.	1268/143	Ref.	575/133	Ref.
	Intermediate	150/20	1.28 (0.70;2.34)	534/98	1.24 (0.95;1.63)	268/75	1.09 (0.82;1.47)
	Unfavorable	62/13	2.33 (1.17;4.62)	272/56	1.48 (1.07;2.04)	127/31	1.15 (0.77;1.71)

Adjusted for: age, sex and education
Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval.

Table 6. Risk of incident Alzheimer's disease according to tertiles of the polygenic risk score

Polygenic risk score tertiles	N/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Low risk (first tertile)	1864/189	Reference	Reference
Intermediate risk (second tertile)	1885/213	1.16 (0.96;1.42)	1.15 (0.95;1.40)
High risk (third tertile)	1811//251	1.53 (1.27;1.85)	1.54 (1.27;1.86)
P for trend		7.82×10^{-6}	7.46×10^{-6}

Model 1 - adjusted for: age, sex and education
Model 2 - additionally adjusted for: parental history of dementia, history of stroke, systolic blood pressure, total and high-density lipoprotein cholesterol
Abbreviations: N=number of individuals at risk, n=number of Alzheimer's disease cases during follow-up, HR=hazard ratio, CI=confidence interval. The log rank test was used to calculate P values. Two-sided P values were uncorrected for multiple testing.

Table 7. Risk of incident Alzheimer's disease while stratifying participants both on tertiles of a polygenic risk score and different modifiable risk factor profiles

Polygenic risk score	Risk factor profile	N/n	HR (95% CI)
Low (Lowest tertile)	Favorable	1191/99	Reference
	Intermediate	478/60	1.11 (0.79;1.56)
	Unfavorable	195/30	1.46 (0.95;2.25)
	P for trend		0.0547
Intermediate (Middle)	Favorable	1230/125	Reference
	Intermediate	454/63	1.22 (0.89;1.68)
	Unfavorable	201/25	1.08 (0.69;1.67)
	P for trend		0.3974
High (Highest tertile)	Favorable	1204/159	Reference
	Intermediate	429/60	0.97 (0.71;1.31)
	Unfavorable	178/32	1.27 (0.85;1.89)
	P for trend		0.9574

Adjusted for: age, sex and education
Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval. The log rank test was used to calculate P values. Two-sided P values were uncorrected for multiple testing.

Table 8. Risk of incident dementia while stratifying participants both on *APOE* and on levels of modifiable risk based on the Ideal Cardiovascular Health metric

APOE-related risk	Risk factor profile	N/n	HR (95% CI)
	Favorable	18/1	Reference
	Intermediate	426/30	1.31 (0.18;9.70)
Low (ε2ε2/ε2ε3)	Unfavorable	443/54	1.93 (2.64;14.11)
	P for trend		0.0942
	Favorable	35/4	Reference
	Intermediate	1871/199	0.80 (0.28;2.13)
Intermediate (ε3ε3)	Unfavorable	1812/253	0.85 (0.31;2.33)
	P for trend		0.2944
	Favorable	20/5	Reference
	Intermediate	849/189	0.72 (0.30;1.77)
High (ε2ε4/ε3ε4/ ε4ε4)	Unfavorable	778/180	0.55 (0.23;1.36)
	P for trend		0.0085

Adjusted for: age, sex and education
Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval. The log rank test was used to calculate P values. Two-sided P values were uncorrected for multiple testing.

Table 9. Risk of incident dementia while stratifying participants both on *APOE* and on their 10-year predicted risk of fatal cardiovascular diseases

APOE-related risk	Risk factor profile	N/n	HR (95% CI)
	Favorable	386/15	Reference
	Intermediate	225/20	1.22 (0.58;2.55)
Low (ε2ε2/ε2ε3)	Unfavorable	256/45	1.73 (0.73;4.06)
	P for trend		0.1866
	Favorable	1539/83	Reference
	Intermediate	991/123	1.34 (0.98;1.83)
Intermediate (ε3ε3)	Unfavorable	1061/237	1.66 (1.16;2.38)
	P for trend		0.0061
	Favorable	734/108	Reference
	Intermediate	480/109	1.01 (0.58;1.28)
High (ε2ε4/ε3ε4/ ε4ε4)	Unfavorable	469/139	0.86 (0.74;1.37)
	P for trend		0.4528

Adjusted for: age, sex and education
Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval. The log rank test was used to calculate P values. Two-sided P values were uncorrected for multiple testing.

Table 10. Health and lifestyle-specific associations with dementia risk

	N/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Abstaining from smoking	5093/790	0.97 (0.80;1.17)	0.97 (0.84;1.18)
Absence of depression	5717/792	0.65 (0.54;0.79)	0.66 (0.54;0.80)
Absence of diabetes	5618/796	0.74 (0.61;0.90)	0.74 (0.61;0.91)
Regular physical activity	3598/434	0.90 (0.78;1.05)	0.91 (0.78;1.06)
Avoiding social isolation	4526/559	1.04 (0.89;1.21)	1.05 (0.90;1.22)
Adherence to a healthy dietary pattern	952/181	1.09 (0.92;1.29)	1.10 (0.93;1.30)

Model 1 - adjusted for: age, sex and education.

Model 2 - additionally adjusted for: parental history of dementia, history of stroke, systolic blood pressure, total and high-density lipoprotein cholesterol

Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval.

Table 11. Associations of individual Ideal Cardiovascular Health components with the risk of dementia

	N/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1. Abstaining from smoking	5093/790	0.97 (0.80;1.17)	0.97 (0.84;1.18)
2. Ideal body mass index	2071/306	1.09 (0.95;1.26)	1.08 (0.94;1.24)
3. Ideal physical activity	3598/434	0.74 (0.61;0.90)	0.74 (0.61;0.91)
4. Adherence to a healthy dietary pattern	952/181	1.09 (0.92;1.29)	1.10 (0.93;1.30)
5. Untreated total cholesterol <5.2 mmol/L	1565/209	0.97 (0.83;1.14)	1.04 (0.88;1.22)
6. Untreated systolic blood pressure <120 mmHg & diastolic blood pressure <80 mmHg	737/95	1.10 (0.90;1.37)	1.09 (0.88;1.35)
7. Fasting plasma glucose <5.5 mmol/L	3013/447	1.00 (0.88;1.14)	1.01 (0.89;1.15)

Model 1 - adjusted for: age, sex and education.

Model 2 - additionally adjusted for: parental history of dementia and history of stroke.

Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval.

Table 12. Associations of the individual SCORE risk equation components with the risk of dementia

	N/n	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Age, per year	6352/915	1.13 (1.12;1.14)	1.13 (1.12;1.14)
Current smoking	1259/125	1.00 (0.81;1.24)	0.99 (0.80;1.23)
Systolic blood pressure, per 10 mmHg	6352/915	1.01 (0.98;1.04)	1.01 (0.98;1.04)
Total cholesterol, per mmol/L	6352/915	1.04 (0.97;1.11)	1.04 (0.97;1.12)

Model 1 - adjusted for: sex.

Model 2 - additionally adjusted for: parental history of dementia and history of stroke.

Abbreviations: n=number of cases, N=number of people at risk, HR=hazard ratio, CI=confidence interval.

Table 13. Baseline characteristics for included and excluded participants of the current study

	Included participants N=6352	Excluded participants N=1433
Age, years	69.1 (8.2)	70.7 (10.6)
Women	3572 (56.2)	956 (66.7)
Educational years, median (IQR)	10 (7-13)	10 (7-13)
Parental history of dementia	427 (6.7)	13 (0.9)
History of stroke	231 (3.6)	67 (4.7)
Body mass index, kg/m^2	27.4 (4.0)	26.9 (3.9)
Systolic blood pressure, mmHg	143 (21)	139 (19)
Diastolic blood pressure, mmHg	77 (11)	80 (13)
Total cholesterol, mmol/L	5.8 (1.0)	5.3 (1.0)
High density lipoprotein cholesterol, mmol/L	1.4 (0.4)	1.3 (0.3)
Fasting glucose, mmol/L	6.0 (1.6)	6.1 (2.1)
Age of dementia diagnosis	83.1 (6.5)	84.2 (6.5)
Modifiable health and lifestyle factors		
No current smoking	5064 (79.7)	92 (79.3)*
Absence of depression	5717 (90.0)	96 (85.0)*
Absence of diabetes	5301 (83.5)	38 (82.6)*
Regular physical activity	3598 (56.6)	1 (7.7)*
Absence of social isolation	4508 (71.0)	79 (66.9)*
Healthy diet score	749 (11.8)	136 (17.2)*

Abbreviations: N=number of people at risk, SD=standard deviation, IQR=interquartile range. Data are shown for non-imputed data. * Percentages shown for available, non-missing data. Data presented as frequency (percent) for categorical values and mean ± SD for continuous variables unless indicated otherwise.

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