



# Impact of cardiovascular risk factors and genetics on 10-year absolute risk of dementia: risk charts for targeted prevention

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## Aims

Dementia is a major global challenge for health and social care in aging populations. A third of all dementia may be preventable due to cardiovascular risk factors. Intensive multi-domain intervention trials targeting primarily cardiovascular risk factors show improved cognitive function in people at risk. Such interventions will, however, be expensive to implement in all individuals at risk and will represent unrealistic economic tasks for most societies. Therefore, a risk score identifying high-risk individuals is warranted.

## Methods and results

In 61 664 individuals from two prospective cohorts of the Danish general population, we generated 10-year absolute risk scores for all-cause dementia from cardiovascular risk factors and genetics. In both sexes, 10-year absolute risk of all-cause dementia increased with increasing age, number of apolipoprotein E (APOE)  $\epsilon$ 4 alleles, number of genome-wide association studies (GWAS) risk alleles, and cardiovascular risk factors. The highest 10-year absolute risks of all-cause dementia seen in smoking women with diabetes, low education, APOE  $\epsilon$ 44 genotype, and 22–31 GWAS risk alleles were 6%, 23%, 48%, and 66% in those aged 50–59, 60–69, 70–79, and 80–100, respectively. Corresponding values for men were 5%, 19%, 42%, and 60%, respectively.

## Conclusion

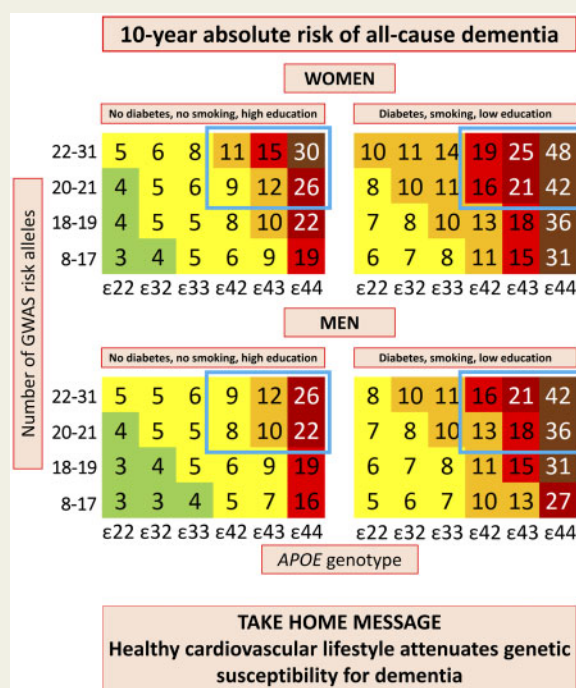
Ten-year absolute risk of all-cause dementia increased with age, APOE  $\epsilon$ 4 alleles, GWAS risk alleles, diabetes, low education, and smoking in both women and men. Ten-year absolute risk charts for dementia will facilitate identification of high-risk individuals, those who likely will benefit the most from an early intervention against cardiovascular risk factors.

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## Graphical Abstract



## Keywords

Cardiovascular risk factors • Dementia • Genetics • Epidemiology

## Introduction

Due to the successes of intervention and prevention in atherosclerotic cardiovascular disease and other common diseases, people now live long enough to develop highly age-dependent dementia disorders. Therefore, dementia is a major global challenge for health and social care in aging populations. A third of old people now die with dementia, and worldwide incidence numbers are projected to be higher than 130 million by 2050.<sup>1</sup> There are no available curative treatments. However, recent estimates from the Lancet Commission based on randomized controlled trials like FINGER<sup>2,3</sup> and preDIVA<sup>4</sup> suggest that a third of all dementia may be preventable,<sup>1</sup> primarily by treating well-established cardiovascular risk factors such as diabetes, hypertension, smoking, and physical inactivity.<sup>5</sup> A key recommendation is to be ambitious about prevention, focusing on interventions to build up resilience and healthier lifestyles,<sup>1</sup> because postponing dementia just for a couple of years would enable many more to reach the end of life without developing dementia.<sup>1,6</sup> The exact nature of prevention and whether it should be applied to all at risk of dementia, or targeted towards high-risk groups, remains unresolved.

Despite drastic increases in dementia prevalence globally, age-standardized incidences are declining in affluent parts of the world,<sup>1</sup>

most likely explained by better control of cardiovascular risk factors and by a general improvement in educational levels during the last decades.<sup>1,7,8</sup> These findings are supported by a comprehensive intervention trial targeting primarily vascular risk factors leading to improved cognitive function in people at risk of dementia.<sup>2,3</sup> However, such intensive and staff-requiring interventions will be expensive to implement in all at risk of dementia and will represent unrealistic economic tasks for most societies. Therefore, a combined risk score that can identify high-risk individuals who likely will benefit the most from targeted preventive interventions is warranted. Because the genetic contribution to late-onset dementia is substantial through the apolipoprotein E (APOE) ε4 allele,<sup>1</sup> and 30 other loci identified more recently in genome-wide association studies (GWAS),<sup>9,10</sup> a combined risk score should consist of these genetic components as well as the most important modifiable risk factors, in order to identify those at the very highest risk.

In the present study, we generated 10-year absolute risk scores for all-cause dementia combining cardiovascular risk factors and genetics. These algorithms were constructed in 61 664 individuals aged 20–100 from two prospective cohorts of the Danish general population, the Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS) and may serve as tools for comprehensive risk stratification to identify high-risk individuals for targeted prevention.

## Methods

The studies were approved by institutional review boards and Danish ethics committees [no (KF) 100.2039/91 and no (KF) 01-144/01] and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all individuals. Individuals in both studies were white and of Danish descent.

### Participants

Copenhagen General Population Study is a prospective study of the Danish general population initiated in 2003 and still recruiting.<sup>11–14</sup> Individuals were selected randomly based on the national Danish Civil Registration System to reflect the adult Danish population aged 20–100. Data were obtained from a self-administered questionnaire reviewed together with an investigator at the day of attendance, a physical examination, and from blood samples including DNA extraction. Genotypes were available on 53 546 individuals aged 20–100. Copenhagen City Heart Study is a prospective study of the Danish general population initiated in 1976–78 with follow-up examinations in 1981–83, 1991–94, 2001–03, and 2011–13.<sup>11–14</sup> Individuals were recruited and examined as in the CGPS. Genotypes were available on 8118 individuals aged 20–100 from the 1991–94 and 2001–03 examinations. Combining the two studies yielded a total of 61 664 individuals, of whom 2158 developed dementia during a median follow-up of 10 years (range = 1–25 years). No individuals were lost to follow-up. Follow-up began at the time of blood sampling (2003 and onwards for CGPS and 1991–1994 or 2001–2003 for CCHS) and ended at occurrence of a dementia event ( $n = 2158$ ), death ( $n = 8788$ ), emigration ( $n = 334$ ), or on 22 March 2017 (last update of the registry), whichever came first.

### Dementia endpoints

In CGPS and CCHS, information on births, deaths, emigrations, and immigrations was collected from the national Danish Civil Registration System. Information on diagnoses of dementia was drawn from the national Danish Patient Registry and the national Danish Registry of Causes of Death. The national Danish Registry of Causes of Death contains data on causes of all deaths in Denmark, as reported by hospitals, forensic medicine, and general practitioners. Alzheimer's disease was International Classification of Diseases (ICD)8 code 290.10 and ICD10 codes F00 and G30. All-cause dementia further included vascular dementia (ICD10 F01) and unspecified dementia (ICD8 290.18; ICD10 F03).

### Genotyping

TaqMan-based (Life Technologies, a part of Thermo Fisher Scientific, Waltham, Massachusetts, USA) or KASP technology-based assays (LGC Genomics, Hoddesdon, Herts, UK) were used to genotype for *APOE* genotypes p. Cys130Arg (rs429358, legacy name Cys112Arg, c.388T>C) and p. Arg176Cys (rs7412, legacy name Arg158Cys, c.526C>T). The presence of p. Cys130Arg and the absence of p. Arg176Cys on the same allele defines the  $\epsilon 4$  allele, whereas the  $\epsilon 2$  allele is defined by the absence of p. Cys130Arg and the presence of p. Arg176Cys on the same allele.<sup>13,15</sup> The rare  $\epsilon 1$  allele is defined by the presence of both variants on the same allele. Standard genotyping methods without phasing cannot determine which allele a variant is located on. Consequently, the identified  $\epsilon 4/\epsilon 2$  individuals can either have the  $\epsilon 1/\epsilon 3$  or the  $\epsilon 4/\epsilon 2$  combination. Due to the rarity of the  $\epsilon 1$  allele, we assume that most individuals will have the  $\epsilon 4/\epsilon 2$  combination. TaqMan-based or KASP technology-based assays were also used to genotype for GWAS hits of *CR1* rs6656401, *BIN1* rs6733839, *CD2AP* rs10948363, *EPHA1* rs11771145, *CLU* rs9331896, *MS4A6A* rs983392, *PICALM* rs10792832, *ABCA7* rs4147929, *HLA-DRB5*-*HLA-DRB1* rs9271192, *PTK2B* rs28834970, *SORL1* rs11218343, *RIN3*

rs10498633, *INPP5D* rs35349669, *MEF2C* rs190982, *NME8* rs2718058, *ZCWPW1* rs1476679, *CELF1* rs10838725, *FERMT2* rs17125944, and *CASS4* rs7274581.<sup>9</sup>

### Cardiovascular risk factors

Cardiovascular risk factors were registered at baseline. Diabetes mellitus was self-reported disease, use of insulin or oral hypoglycaemic agents, non-fasting plasma glucose levels of more than 11 mmol/L (198 mg/dL) and/or a diagnosis of diabetes at baseline from the national Danish Patient Registry. In two sensitivity analyses, diabetes was defined either as (i) non-fasting plasma glucose levels of more than 11 mmol/L (198 mg/dL) at baseline or (ii) self-reported use of insulin or oral hypoglycaemic agents at baseline. Standard hospital assays measured glucose. Hypertension was self-reported use of antihypertensive medication, a systolic blood pressure of 140 mm Hg or greater, and/or a diastolic blood pressure of 90 mm Hg or greater at baseline. In two sensitivity analyses, hypertension was defined either as (i) a systolic blood pressure of 140 mm Hg or greater, and/or a diastolic blood pressure of 90 mm Hg or greater at baseline or (ii) self-reported use of antihypertensive medication at baseline. Smoking was never/ever smoker. Low physical activity was maximum 4 h per week of light physical activity in leisure time. High alcohol intake was self-reported weekly consumption of more than 14 units alcohol/week for women and more than 21 units alcohol/week for men. Low education was <8 years of formal education (equivalent to a maximum of finalized primary school). When analysing midlife cardiovascular risk factors, only individuals aged 40–60 years at baseline were included.

### Statistical analysis

We used Stata/SE v14.0 (Stata Corp, College Station, TX, USA). Probability values <0.001 were given as powers of 10. *P*-values fulfilling a Bonferroni corrected criteria of 0.006 (0.05/8 items = 0.006; 8 items: diabetes, hypertension, smoking, physical activity, education, alcohol intake, *APOE* genotype, and GWAS risk alleles) were marked with an \*. Kruskal–Wallis one-way analysis of variance or Pearson's  $\chi^2$  test were used to evaluate continuous and categorical variables by genotype. Missing data on covariates were imputed from age, sex, and population by multiple imputation.<sup>16</sup> Missing values were <1% for modifiable risk factors. When performing a sensitivity analysis only including individuals with complete data, results were similar to those reported. Combining GWAS identified genotypes,<sup>9</sup> excluding the *APOE* genotype, we generated a genetic score by summing the number of dementia increasing risk alleles in each individual. Subsequently, all individuals were categorized into four genetic score groups of approximately equal size. The score was generated in the total cohort.

Cox proportional hazards regression models with age as time scale (=age adjustment) and left truncation at study examination (delayed entry) were used to estimate hazard ratios for all-cause dementia and Alzheimer's disease as a function of cardiovascular risk factors adjusted for *APOE* genotype and number of GWAS risk alleles. Death or emigration was taken into account as competing events by censoring on death, emigration, and end of follow-up. For Cox regression models, proportionality of hazards over time was assessed by plotting  $-\ln(-\ln[\text{survival}])$  vs.  $\ln(\text{analysis time})$ . There was no suspicion of non-proportionality. In combination with Cox regression models, Least Absolute Shrinkage and Selection Operator (LASSO) regression<sup>17</sup> was further used to select the cardiovascular risk factors for stratification in 10-year absolute risk charts for all-cause dementia. Least Absolute Shrinkage and Selection Operator is helpful in parsing down to the most important terms, while testing all possible interactions of covariates, and thus identifies the most contributory factors in the dataset. Selection criteria were *P*-values < 0.05 from

**Table 1** Characteristics of study individuals by sex and number of GWAS risk alleles

	Women				Men			
	8–17	18–19	20–21	22–31	8–17	18–19	20–21	22–31
No. of risk alleles	8–17	18–19	20–21	22–31	8–17	18–19	20–21	22–31
No. of individuals	9393	9685	8605	6260	7741	7927	7004	5049
Age (years)	57 (47–67)	58 (47–67)	57 (47–67)	58 (47–67)	58 (48–68)	58 (48–67)	58 (48–67)	58 (47–67)
Diabetes (%)	3.2	3.2	3.1	2.9	5.2	5.6	4.8	5.2
Hypertension (%)	52.9	52.6	52.6	51.9	64.9	65.2	65.0	64.5
Smoking (%)	59.2	59.1	60.1	60.9	65.9	67.1	67.0	66.6
Physical inactivity (%)	57.8	57.3	56.5	57.0	47.4	48.4	47.1	47.4
Low education (%)	13.8	13.9	13.3	14.9†	14.7	14.3	15.1	15.0
High alcohol intake (%)	15.3	14.9	14.3	14.6	21.9	21.3	21.7	21.6
APOE genotype								
ε22 (%)	0.7	0.7	0.7	0.7	0.7	0.8	0.7	0.5
ε32 (%)	12.6	12.1	12.4	12.4	12.4	12.9	12.4	12.1
ε33 (%)	55.3	56.0	54.7	55.6	56.5	55.9	55.8	57.3
ε42 (%)	2.9	2.6	3.2	3.0	2.8	3.1	2.7	2.8
ε43 (%)	25.6	25.7	26.1	25.2	24.8	24.6	26.0	24.9
ε44 (%)	2.9	3.0	2.9	3.2	2.8	2.7	2.5	2.5

Values are numbers, median (interquartile range) or per cent, and are from the day of enrolment (2003 and onwards for the CGPS and 1991–94 or 2001–03 for the CCHS). *P* for trend was calculated using Kruskal–Wallis one-way analysis of variance with ties or Pearson's  $\chi^2$ -test. †*P* < 0.05.

Cox regressions and/or delta Extended Bayesian Information Criteria (EBIC) values  $\geq 10$  from LASSO regressions for all but one covariate (smoking in men where we allowed a delta EBIC = 6).

Ten-year absolute risks of all-cause dementia were calculated using competing risk regression based on Fine and Gray proportional sub-hazards model,<sup>18</sup> to account for the possibility of death or emigration as competing events. The Fine and Gray proportional sub-hazards model was chosen because a competing event prevents the event of interest, which is highly relevant with diseases of late life, while censoring merely obstructs the observation of the event of interest. When stratifying on midlife hypertension, we restricted the analyses to individuals aged 40–60 years at baseline. Because our focus for this study was dementias in late life, 10-year absolute risks of all-cause dementia were shown for individuals at or above 50 years. Twenty-year absolute risks of all-cause dementia were calculated when stratifying on midlife hypertension. Discriminative accuracy of 10- and 20-year absolute risk models stratified on modifiable risk factors was tested using Gray's test.

## Results

Table 1 shows baseline characteristics of the 61 664 individuals enrolled in the study by number of risk alleles for all-cause dementia and Alzheimer's disease from GWAS.

### Cardiovascular risk factors at all ages and at midlife, and risk of dementia

Multifactorially adjusted hazard ratios for all-cause dementia for diabetes by three definitions, hypertension, smoking, low physical activity, low education, and high alcohol intake for all ages (top three panels) and midlife (bottom three panels) are shown in Figure 1.

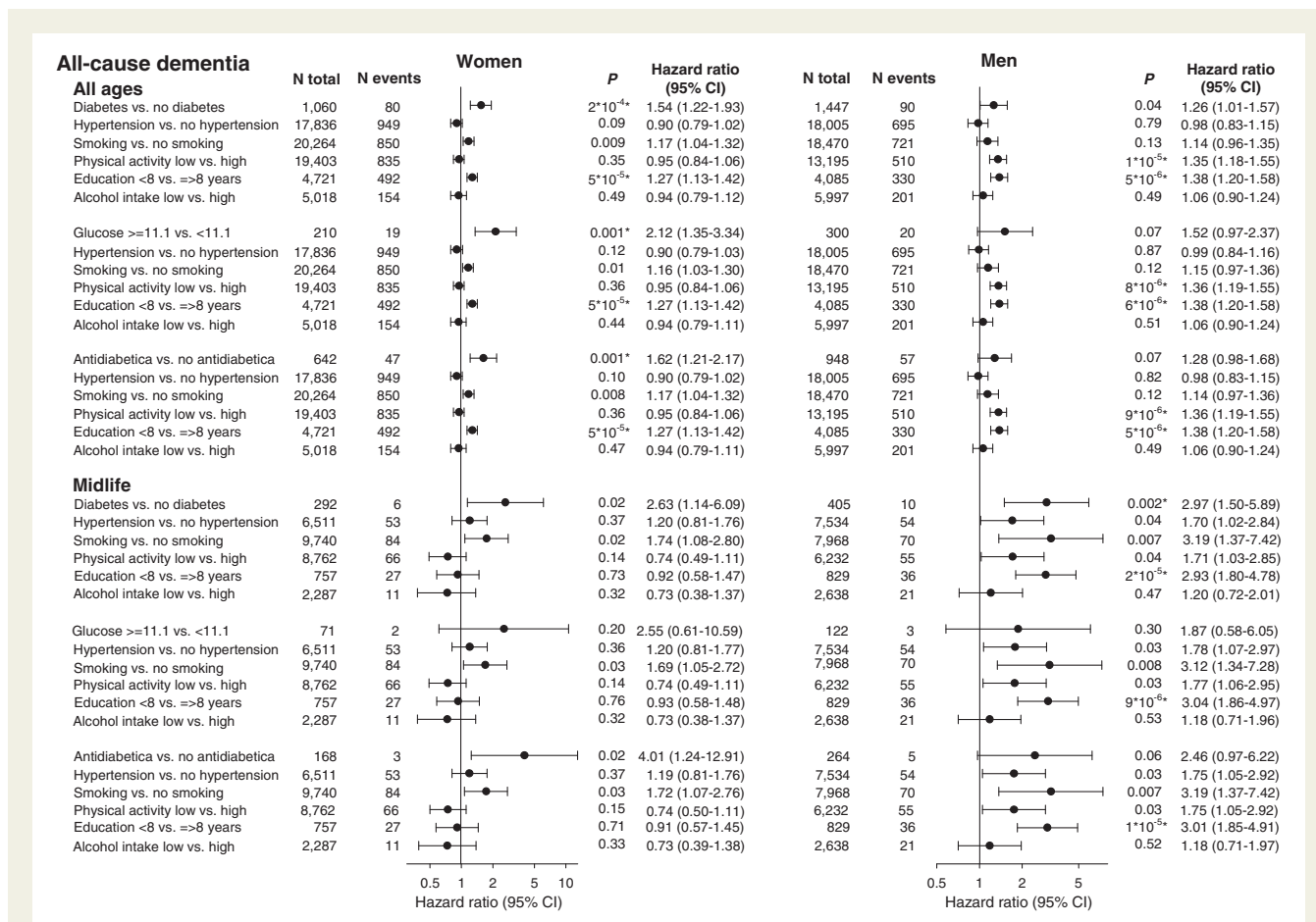
For women, the modifiable risk factors with the highest hazard ratios for all ages were diabetes, smoking, and low education with

hazard ratios of 1.54 (95% CI 1.22–1.93) for diabetes vs. no diabetes, 1.17 (1.04–1.32) for smoking vs. no smoking, and 1.27 (1.13–1.42) for low vs. high education (Figure 1, top panel, left column). Two other definitions of diabetes are given in Figure 1, 2nd and 3rd panels, left column, for all ages and for midlife.

For men, the modifiable risk factors with the highest hazard ratios for all ages were diabetes, low physical activity, and low education with hazard ratios of 1.26 (1.01–1.57) for diabetes vs. no diabetes, 1.35 (1.18–1.55) for low vs. high physical activity, and 1.38 (1.20–1.58) for low vs. high education (Figure 1, top panel, right column). Two other definitions of diabetes are given in Figure 1, 2nd and 3rd panels, right column, for all ages and for midlife.

For women in midlife, the modifiable risk factors with the highest hazard ratios were diabetes and smoking with hazard ratios of 2.63 (1.14–6.09) for diabetes vs. no diabetes and 1.74 (1.08–2.80) for smoking vs. no smoking (Figure 1, 4th panel, left column). For men in midlife, the modifiable risk factors with the highest hazard ratios were diabetes, smoking, and low education with hazard ratios of 2.97 (1.50–5.89) for diabetes vs. no diabetes, 3.19 (1.37–7.42) for smoking vs. no smoking, and 2.93 (1.80–4.78) for low vs. high education (Figure 1, 4th panel, right column). In midlife men, hypertension and low physical activity also contributed to risk with hazard ratios of 1.70 (1.02–2.84) for hypertension vs. no hypertension and 1.71 (1.03–2.85) for low physical activity vs. high physical activity.

Corresponding multifactorially adjusted hazard ratios for all-cause dementia for cardiovascular risk factors with hypertension by three different definitions showed similar patterns (Supplementary material online, Figure S1). Multifactorially adjusted hazard ratios for Alzheimer's disease are shown in Supplementary material online, Figures S2 and S3.



**Figure 1** Risk of all-cause dementia as a function of cardiovascular risk factors at all ages and during midlife. Hazard ratios were multifactorially adjusted for age (as time scale), APOE genotype, number of GWAS risk alleles, and the listed modifiable risk factors. Analyses in the lower three panels were restricted to individuals aged 40–60 years at baseline. P from Cox regression. P-values fulfilling a Bonferroni corrected criteria of 0.006 are marked with an \*. For APOE genotype and number of GWAS risk alleles P was for trend. APOE, apolipoprotein E gene; APOE genotype, ε2/ε3/ε4 APOE genotype; CI, confidence interval; GWAS, genome-wide association study.

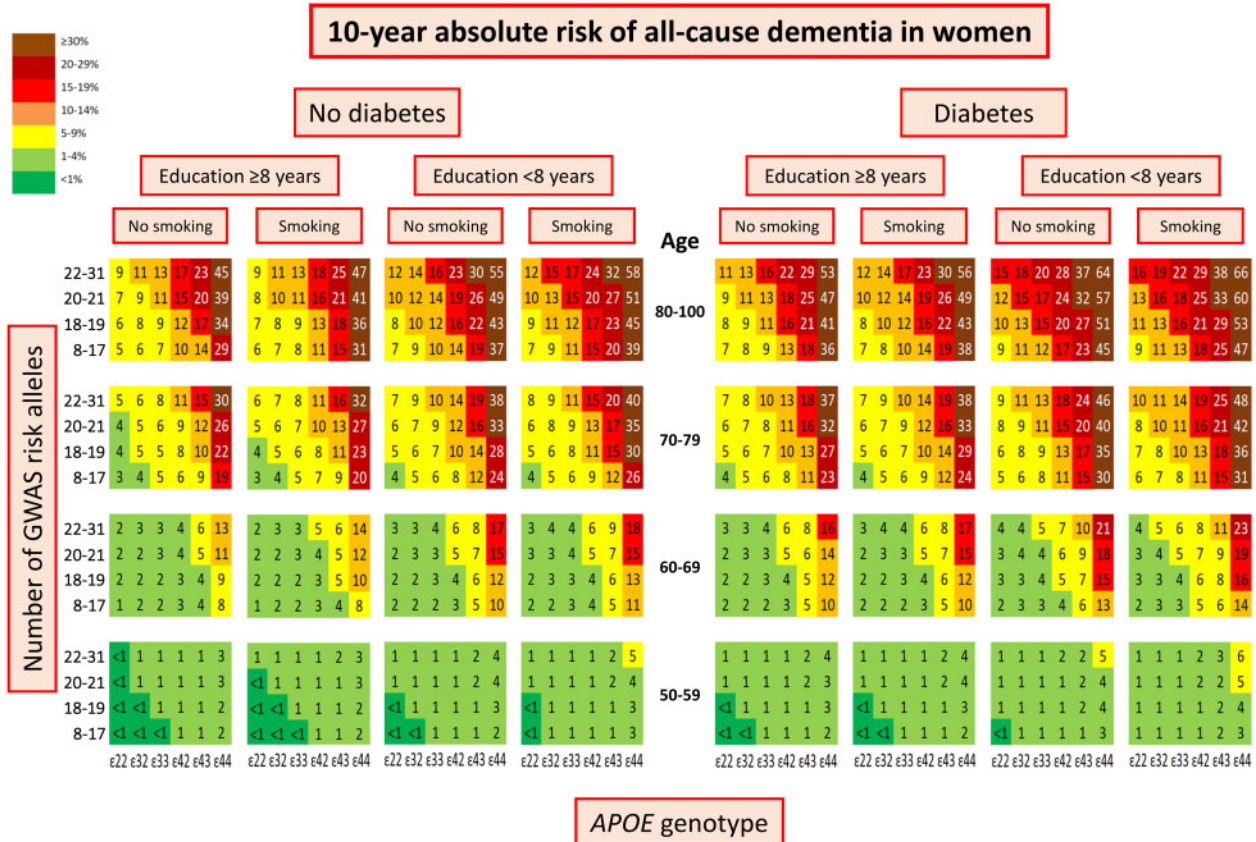
### Selection of cardiovascular risk factors for 10-year absolute risk charts for all-cause dementia

A combined strategy for selecting cardiovascular risk factors for 10-year absolute dementia risk was based on results from multifactorially adjusted Cox models and LASSO regressions. A priori we chose three main stratifications: sex, age, and diabetes, as these are well-established strong independent predictors of all-cause dementia. We then further stratified on education, APOE genotype and GWAS risk alleles, because these were both strong independent predictors in Cox models, as well as contributory factors in LASSO regressions. Finally, we stratified on smoking, because smoking was an independent predictor of dementia in midlife for both women and men and a contributory factor in LASSO regressions. No interaction terms from LASSO regressions between covariates appeared to contribute. In sensitivity analyses, we additionally stratified on alcohol intake and physical activity, because these two covariates either contributed to the Cox or the LASSO model in one sex or in both.

### Ten-year absolute risk of dementia by genetics and cardiovascular risk factors

In women 10-year absolute risk of all-cause dementia stratified on diabetes status, education, and smoking status increased with increasing age, number of APOE ε4 alleles and number of GWAS risk alleles (Figure 2). The highest 10-year absolute risk of 66% was seen in women aged 80–100, with APOE ε44 genotype, 22–31 GWAS risk alleles, diabetes ( $P = 3 \times 10^{-17}$ \* for diabetes status as discriminating factor), low education ( $P = 6 \times 10^{-98}$ \* for educational level as discriminating factor), and smoking ( $P = 0.02$  for smoking status as discriminating factor) (Figure 2, first right column). Corresponding 10-year absolute risk in men was 60% ( $P = 3 \times 10^{-18}$ \* for diabetes status as discriminating factor,  $P = 4 \times 10^{-74}$ \* for educational level as discriminating factor, and  $P = 1 \times 10^{-17}$ \* for smoking status as discriminating factor) (Figure 3, first right column). Stratifications on alcohol intake and physical activity instead of smoking are shown in Supplementary material online, Figures S4–S7. Alcohol intake did not discriminate 10-year absolute risk of all-





**Figure 2** Ten-year absolute risk of all-cause dementia in women. Ten-year absolute risk is read by identifying age group, diabetes status, educational level, smoking status, APOE genotype, and number of GWAS risk alleles. Diabetes status, educational level, and smoking status had the highest hazard ratios by Cox regressions and/or were the best discriminating factors in LASSO regressions. APOE, apolipoprotein E gene; APOE genotype, ε2/ε3/ε4 APOE genotype; GWAS, genome-wide association study.

cause dementia ( $P=0.10$  for women,  $P=0.34$  for men), whereas physical activity did ( $P=3*10^{-5}$ \* for women,  $P=2*10^{-8}$ \* for men).

### Twenty-year absolute risk of dementia by midlife hypertension status

When addressing midlife hypertension, by limiting the analysis to individuals aged 40–60 years at baseline, 20-year absolute risk of all-cause dementia stratified on midlife hypertension increased with increasing age, number of APOE ε4 alleles and number of GWAS risk alleles, to a maximum of 17% for women aged 50–60, with the APOE ε44 genotype, 22–31 GWAS risk alleles, and midlife hypertension ( $P=0.006$ \* for midlife hypertension as discriminating factor) (Figure 4, second left column). The corresponding value in men was 14% ( $P=0.002$ \*) (Figure 4, first right column).

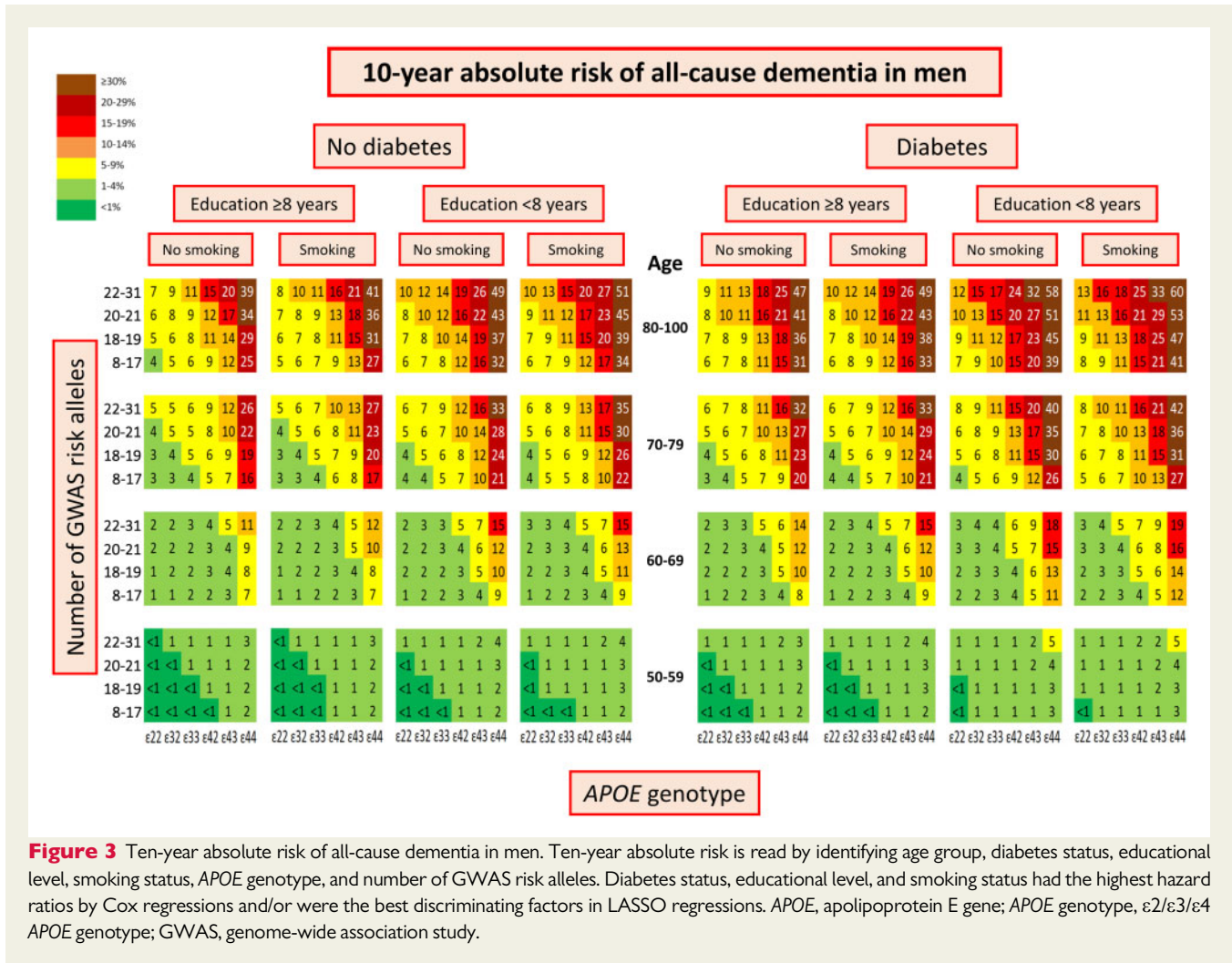
### Ten-year absolute risk of dementia separately in APOE ε44 homozygotes, ε43 heterozygotes, and ε33 homozygotes

In APOE ε44 homozygotes, 10-year absolute risk varied from 48% to 19% in women aged 70–79, depending on the burden of

GWAS risk alleles and modifiable risk factors (women aged 70–79 with APOE ε44, diabetes, low education, smoking, and 22–31 GWAS risk alleles vs. women aged 70–79 with APOE ε44, no diabetes, high education, no smoking, and 8–17 GWAS risk alleles) (Figure 2). Corresponding 10-year absolute risk in men varied from 42% to 16% (Figure 3).

In LASSO regressions only including ε44 homozygotes, diabetes and education were the best discriminating modifiable risk factors. In women, 10-year absolute risk of all-cause dementia stratified on diabetes status and education increased with increasing age. The highest 10-year absolute risk of 43% was seen in women aged 80–100 with diabetes ( $P=0.006$ \* for diabetes status as discriminating factor) and low education ( $P=1*10^{-7}$ \* for educational level as discriminating factor) (Figure 5, 2nd left column). Corresponding 10-year absolute risk in men was 36% ( $P=0.96$  for diabetes status as discriminating factor,  $P=2*10^{-7}$ \* for educational level as discriminating factor) (Figure 5, first right column).

In APOE ε43 heterozygotes and APOE ε33 homozygotes, 10-year absolute risk of all-cause dementia stratified on the best discriminating risk factors from LASSO regressions are shown in [Supplementary material online, Figures S8 and S9](#). In ε43



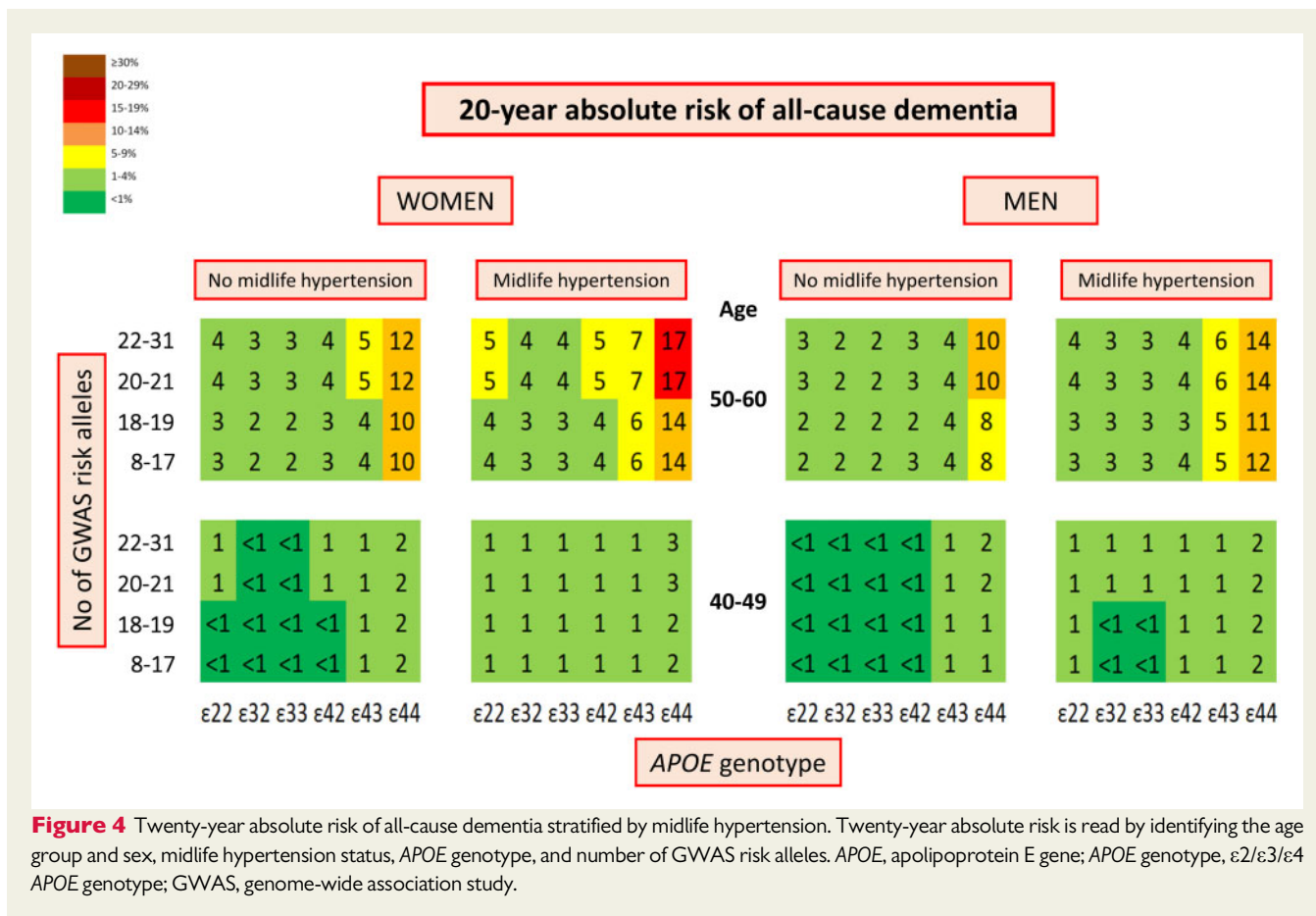
**Figure 3** Ten-year absolute risk of all-cause dementia in men. Ten-year absolute risk is read by identifying age group, diabetes status, educational level, smoking status, APOE genotype, and number of GWAS risk alleles. Diabetes status, educational level, and smoking status had the highest hazard ratios by Cox regressions and/or were the best discriminating factors in LASSO regressions. APOE, apolipoprotein E gene; APOE genotype, ε2/ε3/ε4 APOE genotype; GWAS, genome-wide association study.

heterozygotes, diabetes and education remained as discriminating factors in women, whereas education remained in men (diabetes:  $P = 1 \times 10^{-4}$ \*, education:  $P = 1 \times 10^{-62}$ \* in women; diabetes:  $P = 0.14$ , education:  $P = 4 \times 10^{-24}$ \* in men). For ε33 homozygotes, diabetes and education remained as discriminating factors in women, whereas diabetes, education and physical activity remained in men (diabetes:  $P = 3 \times 10^{-8}$ \*, education:  $P = 8 \times 10^{-49}$ \* in women; diabetes:  $P = 6 \times 10^{-15}$ \*, education:  $P = 4 \times 10^{-41}$ \*, physical activity:  $P = 2 \times 10^{-6}$ \* in men).

## Discussion

The principal findings of this study are that 10-year absolute risk of all-cause dementia increase with increasing age, number of APOE ε4 alleles, GWAS risk alleles, and with diabetes, low education, and smoking. Physical inactivity also contributed, especially in men. These findings are timely and facilitate identification of high-risk individuals, those that are anticipated to benefit the most from targeted prevention (*Take home figure*).

To the best of our knowledge, this is the first study to assess 10-year absolute risk of dementia by age, APOE genotype, GWAS risk alleles, and cardiovascular risk factors taking risk of death as a competing event into account in large prospective cohorts of the general population. Because we found diabetes, smoking, low education, physical activity, and alcohol intake to be the strongest modifiable risk factors for all-cause dementia in Cox and LASSO regressions, we stratified the 10-year absolute risk on these risk factors. The Cox model has the advantage of estimating the independent contribution of each covariate, whereas LASSO regression has the advantage of parsing down to the most important terms, while testing all possible interactions of covariates, and thus helps identifying the most contributory factors in the dataset. Diabetes, low education, and smoking eventually turned out to be the discriminatory modifiable risk factors in Fine and Gray analyses of 10-year absolute risk, and diabetes and low education when ε44 homozygotes, ε43 heterozygotes, and ε33 homozygotes were assessed separately. Furthermore, we observed that both untreated and treated diabetes were predictors of all-cause dementia in all ages and midlife, whereas hypertension in accordance with the literature<sup>1</sup> was only a predictor in midlife, when assessed as

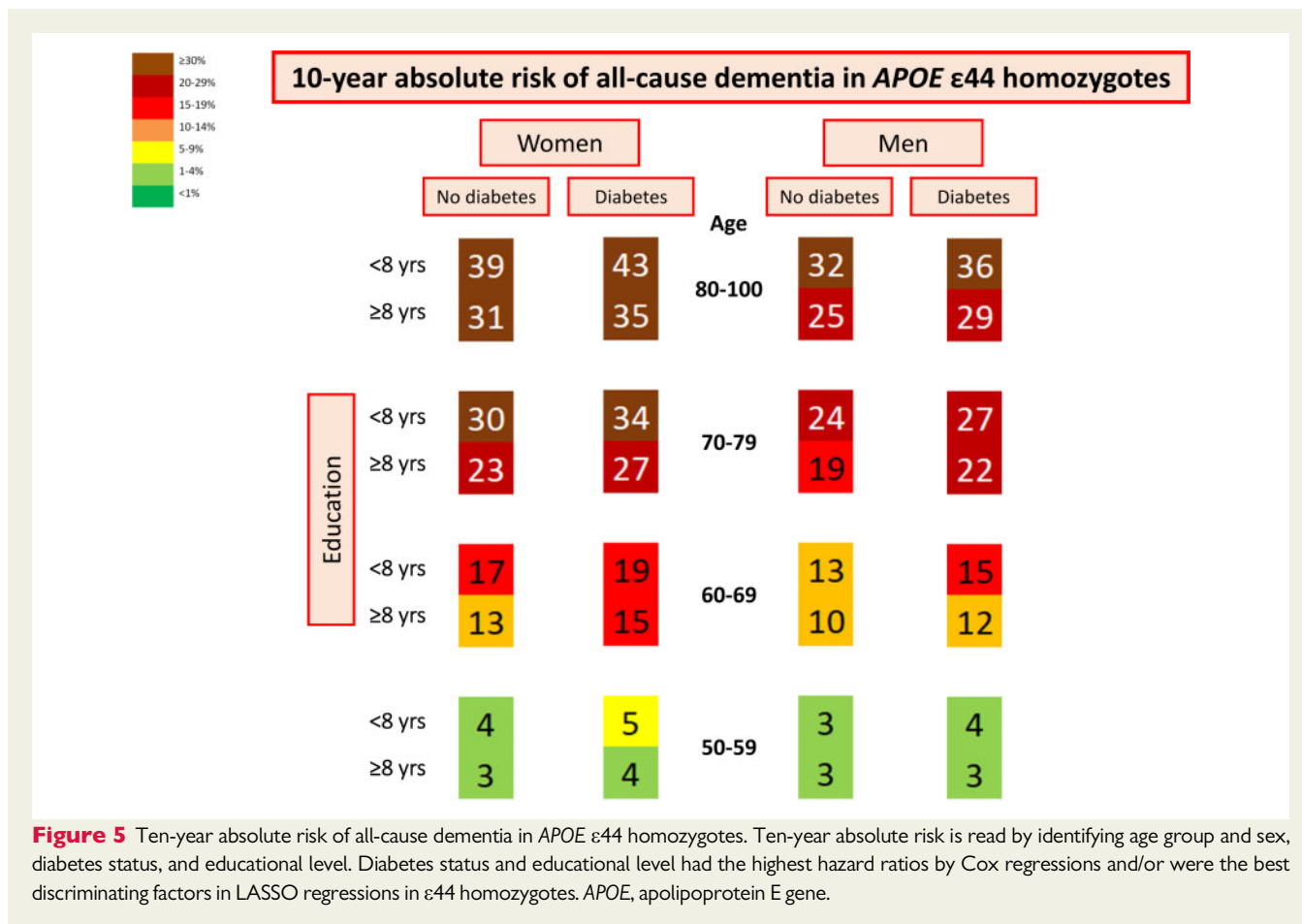


the combined covariate or as measured blood pressure. The present findings for the contribution of age and genetic variants are in accordance with a recent report from the Rotterdam study,<sup>19</sup> summarizing that common genetic variants with small individual effects jointly modify the risk and age at onset of all-cause dementia and Alzheimer’s disease, particularly in APOE ε4-carriers (homozygotes and heterozygotes combined). To facilitate the usability of risk scores, we now provide stratification by age, sex, cardiovascular risk factors, GWAS risk alleles, and by exact APOE genotype representing specific individuals. Since 2006 several risk prediction models for dementia, mainly focusing on cardiovascular risk factors, blood biomarkers, cognitive testing, and brain imaging, have been published.<sup>1,8,20,21</sup> These risk scores are based on scoring systems summing up points for the different test results, cardiovascular risk factors, age, sex, and in some cases APOE genotype. In contrast, the present risk score is similar to the widely used SCORE<sup>22</sup> for risk of cardiovascular disease and takes risk of death as a competing event into account, which is crucial for diseases of late life.

The mechanisms behind how cardiovascular risk factors affect dementia are not well-established; however, suggestive evidence exists that will be reviewed in the following. Diabetes is strongly associated with increased risk of dementia.<sup>7</sup> One potential mechanism may be that peripheral insulin anomalies cause a decrease in brain insulin production, which can impair amyloid clearance.<sup>1</sup> Also,

inflammation and high blood glucose concentrations are suggested as potential mechanisms by which diabetes impairs cognition.<sup>1</sup> Low educational level, equivalent to a maximum of finalized primary school, as a potential modifiable risk factor has shown the most consistent association with risk of dementia.<sup>23,24</sup> Satizabal et al.<sup>25</sup> examined dementia incidences in the Framingham Heart Study and found a declining incidence over three decades, but only among people who had at least a high school diploma. It is a widespread opinion that this is due to higher cognitive reserve in individuals with higher level of education. Individuals with higher educational level tolerate more severe brain pathology without developing clinical dementia compared with individuals with lower educational level.<sup>1,26</sup> However, it is also likely that those with low education have a less favourable lifestyle than those with high education, potentially explaining a part of the high risk of dementia in individuals with low vs. high education. Smoking associates with increased risk of dementia,<sup>24,27</sup> and is likely mediated by cardiovascular pathology and the content of neurotoxins in cigarette smoke.<sup>1,28</sup> Midlife hypertension is consistently associated with increased risk of dementia<sup>1,5,29</sup>—an association we can confirm at least for men in the present study—and is suggested to be through increased risk of cerebrovascular disease and the metabolic syndrome.<sup>1</sup> Physical activity is inversely associated with risk of dementia,<sup>1,5,30</sup> an association mainly explained by cardiovascular risk factors.<sup>1,30</sup> Finally, the



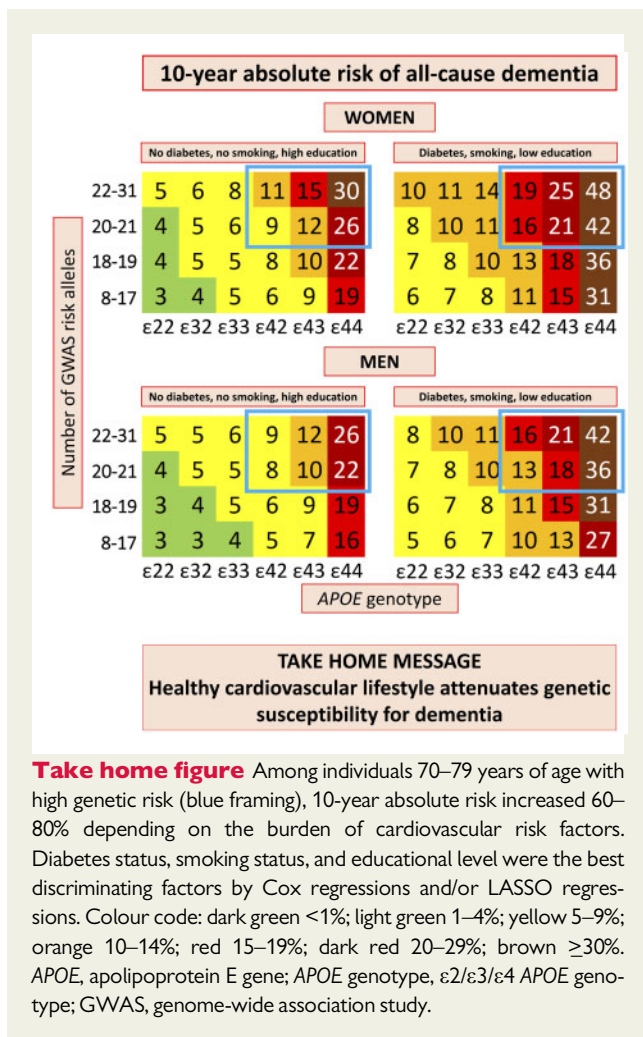


current evidence for the association between alcohol intake and risk of dementia is unclear.<sup>1,7</sup>

Intervention trials to prevent dementia has shown that decreasing the risk of dementia requires extensive multidomain interventions.<sup>2,4,31</sup> The preDIVA trial ‘provided modestly enhanced care to non-selected or non-targeted patients already connected to medical practice’ to identify and try to reduce vascular risk of dementia, however, without success.<sup>4</sup> In contrast, in the FINGER trial—a proof-of-concept randomized controlled trial with intensive, multidomain intervention on nutritional guidance, exercise, cognitive training, and management of metabolic and cardiovascular risk factors applied to at-risk elderly people from the general population—the participants in the intervention group showed improved or maintained cognitive function after 2 years of intervention independent of baseline characteristics.<sup>2,3</sup> This intensive multidomain intervention will, however, most likely be an unrealistic economic burden for many societies to implement in all individuals at risk of dementia. Therefore, the implementation of a combined genetic- and risk factor score identifying high-risk individuals who are likely to benefit the most from a targeted preventive intervention is in high demand. Based on the present data, we suggest that focus must be on raising the educational level for children, adolescents, and young adults, and that a targeted preventive intervention on cardiovascular risk factors starts at age 60

at the latest. Furthermore, a general aggressive healthy lifestyle should be reinforced throughout the life course.

For cardiovascular disease, implementation of genetic risk scores for primary prevention is anticipated to reach clinical practice in the near future.<sup>32</sup> The genetic contribution to common forms of age-related dementia is much stronger than for cardiovascular disease, exemplified very clearly by the well-known *APOE* effect but also by the additive effect of other common risk alleles.<sup>10</sup> Since the genetic contribution to dementia is stronger than the contribution from modifiable risk factors—in sharp contrast to cardiovascular disease—polygenic information is key for a robust dementia risk score. The selection of risk alleles for the score was based on a conservative judgement, where the strongest genetic hits that were validated in both testing and replication samples were chosen.<sup>9</sup> For future updates of the score, additional risk alleles from recent GWAS may be worthwhile to include,<sup>10,33</sup> although these probably will have minor contributions. Reassuringly, the use of genetic information for risk prediction and targeted intervention is anticipated to be received well, as a previous study revealed that knowing your *APOE* genotype in relation to risk of Alzheimer’s disease does not result in emotional distress, even with no available treatment.<sup>34</sup> Importantly, we now show that among *APOE* ε44 homozygotes 10-year absolute risk



can vary substantially depending on the burden of additional genetic risk variants and cardiovascular risk factors.

The present study has potential limitations and strengths that need to be addressed. As events are based on ICD registry codes from hospitals and death certificates, only individuals with a dementia diagnosis as a cause or contributing cause of death, or those referred to hospitals, are included in the present study, in contrast to research studies examining all participants using study physicians and standardized diagnostic methods.<sup>35</sup> The use of hospital record data, however, reduces attrition bias.<sup>30</sup> Even though the national Danish registries are regarded among the best of its kind,<sup>36,37</sup> and the quality of the Danish registry-based dementia diagnoses previously has been validated,<sup>38</sup> the use of registry-based diagnoses suffer from potential underdiagnosis. We ensured, by scrutinizing department codes for all events, that 91–93% of all-cause dementia diagnoses were given from departments of internal medicine, dementia clinics, other neurological outpatient clinics, departments of neurology and neurosurgery, or in- and outpatient clinics at departments of geriatrics.<sup>15</sup> This information together with the fact that APOE ε44 vs. ε33 homozygotes have 8- to 10-fold risk of Alzheimer's disease in the present populations<sup>13,39</sup> provide confidence that the present Alzheimer's disease

diagnosis is acceptable to use. Strengths of our study are the prospective design and the large, well-characterized, ethnically homogeneous cohorts of the general population with no losses to follow-up, and the use of competing risk regression. Ethnically homogeneity may, however, lead to limited applicability for individuals of other ethnicities, supporting the need for more extensive studies in diverse populations.

In conclusion, in combined and easily applicable 10-year absolute risk scores of all-cause dementia, we find that risk increases with increasing age, number of APOE ε4 alleles, GWAS risk alleles, and with diabetes, low education, and smoking. These findings are timely and may serve as tools for comprehensive risk stratification to facilitate efficient preventive and curative trials in high-risk groups of individuals, those that likely will benefit the most from interventions.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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