## RESEARCH

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# A single risk assessment for the most common diseases of ageing, developed and validated on 10 cohort studies

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## Abstract

**Background** We aimed to develop risk tools for dementia, stroke, myocardial infarction (MI), and diabetes, for adults aged  $\geq$  65 years using shared risk factors.

**Methods** Data were obtained from 10 population-based cohorts (*N*=41,755) with median follow-up time (years) for dementia, stroke, MI, and diabetes of 6.2, 7.0, 6.8, and 7.4, respectively. Disease-free participants at baseline were included, and 22 risk factors (sociodemographic, medical, lifestyle, laboratory biomarkers) were evaluated. Two risk tools (DemNCD and DemNCD-LR based on Fine and Gray sub-distribution and logistic regression [LR], respectively) were developed and validated. Predictive accuracies of these risk tools were assessed using Harrel's C-statistics and area under the curve (AUC) and 95% confidence interval (CI). Model calibration was conducted using Hosmer–Lemeshow goodness of fit test along calibration plots.

**Results** Both the DemNCD and DemNCD-LR resulted in similar predictive accuracy for each outcome. The overall AUC (95% Cl) for dementia, stroke, MI, and diabetes risk tool were 0.68 (0.65, 0.70), 0.58 (0.54, 0.61), 0.65 (0.61, 0.68), and 0.68 (0.64, 0.72), respectively, for males. For females, these figures were 0.65 (0.63, 0.67), 0.55 (0.52, 0.57), 0.65 (0.62, 0.68), and 0.61 (0.57, 0.65).

**Conclusions** The DemNCD is the first tool to predict both dementia and multiple cardio-metabolic diseases using comprehensive risk factors and provided similar predictive accuracy to existing risk tools. It has similar predictive accuracy as tools designed for single outcomes in this age-group. DemNCD has the potential to be used in community and clinical settings as it includes self-reported and routinely available clinical measures.

Keywords Risk factors, Risk tool, Primary prevention, Dementia, Stroke, Diabetes, Heart attack, Risk prediction

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### Background

Dementia is a global health problem, currently affecting over 55 million people worldwide, two thirds of whom reside in low- and middle-income countries and risk reduction is a key public health priority [1, 2]. Cardiometabolic disease, e.g., stroke, myocardial infarction, and diabetes, are strong independent risk factors for dementia [3-6]. A recent study has reported that dementia risk associated with high cardio-metabolic multimorbidity was three time greater than that associated with genetic risk [3]. Moreover, researchers have identified key modifiable risk factors for dementia [4, 7] including physical inactivity, unhealthy diet, excessive alcohol intake, smoking, hypertension, high cholesterol, obesity, sleep problems, and depression, which are also shared with these non communicable diseases (NCDs) among older adults in varying degree with each gender [8]. Therefore, dementia prevention strategies are now focused on prevention of these cardiometabolic disease to achieve maximum benefit [2, 4].

Validated risk factor assessment tools play a cruicial role in raising awareness of risk factors for chronic disease. They may allow for the early identification of high-risk individuals and population groups and guide health professionals' recommendations for interventions to improve lifestyle habits. Although several independent risk tools for dementia [9–11], stroke [12–14], MI [15–17], and diabetes [18] have been developed, recent studies have explored the potential of cardiovarascular risk tools in predicting dementia [19, 20]. This is based on evidence that vascular risk factors consistently linked to cognitive decline [21]. However, such approach may not incorporate all the modifiable risk factors of dementia identified by the recent Lancet commission report [4].

Additionally, awareness of the shared risk factors between dementia and NCDs among general population remains low [22, 23]. Therefore, a unified risk assessment tool that incorporates modifiable risk factors for these NCDs would be efficient in increasing risk awareness and more cost effective than assessing risks for each individual NCD [24]. Such a tool could better support clinicians in their efforts at health promotion by showing the pleiotropic benefits of lifestyle changes on patients' health. A recent report also indicated a positive views among general practionner in adopting such tool in their practices [25]. It may guide policy-makers in their development of population-based prevention strategies.

We aimed to develop a new risk prediction tool called "DemNCD" (Dementia and other NCDs) to predict the risks of dementia, stroke, diabetes, and MI in older adults (age  $\geq$  65 years) using a broad range of shared risk factors. DemNCD was derived from analysis of 10 prospective cohort studies (to provide sufficient sample size) that measured risk factors for the four outcomes of interest and incident disease during follow-up.

### Methods

### Data and participants

Data were obtained from prospective population-based cohorts identified through searches of consortia websites, databases, and consultation with experts. Details of the study methods and procedures are described elsewhere [26]. Briefly, 10 cohorts were selected based on the availability of a clinical diagnosis of dementia and other NCDs, risk factors, length of follow-up time, sample size, and availability of data from the study custodians. The cohorts included the Atherosclerosis Risk in Communities (ARIC) [27], the Cardiovascular Health Study (CHS) [28], the Framingham Heart Study (FHS) [29], the MRC Cognitive function and Ageing Studies (both MRC CFAS-I and CFAS-II) [30, 31], the Sydney Memory and Aging Study (MAS) [32], the Maastricht Aging Study (MAAS) [33], the Health and Retirement Study-Aging, Demographics, and Memory Study (HRS ADAMS) [34], the RUSH Memory and Aging project (MAP) [35], and the Singapore Longitudinal Ageing Study-I (SLAS-I) [36]. Additional file 1: Section S1 describes each study, including study recruitment and longitudinal timelines. Additional details on the selection of studies are also available in the DemNCD protocol paper [26]. The baseline age distribution varied across the studies with CHS, CFAS I, and CFAS II including data only for adults aged 65 and above. Therefore, we included participants who were aged  $\geq$  65 years at inception or time of first assessment for dementia and other NCDs. We therefore considered subsets of these cohorts with participants aged  $\geq$  65 years for analysis. Covariates from each dataset were harmonized to allow merging. In the pooled sample, 41,755 older participants were available from 10 cohorts for analysis.

### Outcomes

The outcomes for the risk prediction model included diabetes, stroke, MI, and dementia. Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-III-R, IV) or other well-established criteria that included the Mental State – Automated Geriatric Examination for Computer Assisted Taxonomy (GMS-AGECAT), criteria of National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's disease and Related Disorders Association. For diabetes, stroke, and MI, a clinical diagnosis was preferred but otherwise a self-reported diagnosis was used (Additional file 1: Table S1).

### Predictors

We used a four-stage process to select predictors (see Additional file 1: Fig. S1). Stage I included selecting potential predictors from the latest comprehensive systematic reviews [7, 37-43], Lancet Commissions [1, 44], and WHO Guidelines [2]. Stage II comprised additional predictors identified from existing published risk tools for each outcome [12, 45–51]. At stage III, all predictors identified in the previous two stages were reviewed and ranked independently by subject matter experts into order of importance (see [26]). Finally, all the identified predictors were checked for availability in the datasets (Additional file 1: Table S2). Overall, 22 demographic (age, sex, and education), medical (self-reported high blood pressure, depression, obesity using measured body mass index (BMI), atrial fibrillation (AF), total cholesterol and both high- and low-density lipoprotein, traumatic brain injury (TBI), left ventricular hypertrophy, chronic kidney disease and hearing loss), and lifestyle (cigarette smoking, alcohol consumption, weekly fruit and vegetable intake, fish intake, loneliness, low cognitive engagement, sleep problems and physical inactivity) predictors were selected based on their availability in the cohort datasets. Left ventricular hypertrophy and chronic kidney disease were excluded from the analysis due to their unavailability in most ( $\geq$ 7) of the datasets. Additional file 1: Table S3 reports definitions of the covariates used in the data harmonization. Selection of predictors was primarily based on routinely collected information, focusing on data readily available to clinicians and individuals, that provide ready targets for intervention. As a result, biomarkers that are rarely available (e.g., APOE e4) were not included.

### Statistical analysis

The pooled dataset was randomly split into two parts using 65:35 ratios for development (model data) and validation data. Proportionate representation of age, sex, and study cohort was ensured in the development and validation samples. In the model dataset, a large amount of missing data was observed due to complete non-response (absence of variables) and partial missingness. Multivariate normal multiple imputation was used to impute missing values in the model dataset. Cohort-specific indicator variables along with all the outcomes and covariates in the analysis models were used as covariates in the imputation model. Twenty imputed datasets were considered in the model dataset based on von Hippel et al. guidelines [52]. Following imputation, the Fine and Gray sub-distribution model was used [53] to regress the sub-distribution hazards of respective outcomes to the model data according to the following models:

 $\lambda_{stoke}(t) = \lambda_{stroke,0}(t)\exp(\beta * X + \beta_1 * diabetes + \beta_2 * MI)$ 

 $\lambda_{MI}(t) = \lambda_{MI,0}(t)\exp(\gamma * X + \gamma_1 * diabetes + \gamma_2 * stroke)$ 

$$\lambda_{diabetes}(t) = \lambda_{diabetes,0}(t) \exp(\delta * X)$$

with death as competing event to the imputed datasets stratified by cohorts and sex, where X=(age, education, obesity, alcohol consumption, smoking, hypertension, cholesterol, high- and low-density lipoprotein, depression, fish serve, fruits and vegetable intake, TBI, loneliness, insufficient physical activity, AF, sleep problems, hearing loss). We also included cognitive engagement as a covariate for the dementia outcome. Only individuals with known incident outcome status were included in the model.

For each sex, the resultant cohort-specific regression coefficients were then combined using Rubin's rule [54]. These sex and cohort specific regression coefficients for each of the risk factors were further aggregated across different cohorts through random-effects meta-analysis. In this step, regression coefficients of the covariates were only included in the meta-analysis if covariate information were available for a given cohort. This restriction was imposed to avoid an influence of large cohorts on the imputed values of nonresponse variables. The final regression coefficients were then converted to obtain point-based scoring algorithms for each sex and outcome [55]. The sexspecific point-based risk scores were then validated using the validation sample. The accuracy of the risk scores for identifying participants at risk of dementia and other outcomes were quantified by calculating the Harrel'C statistics [56] and associated 95% CIs. Cut-off values (quantile ranks) for the risk scores were compared relative to sub-distribution hazards ratios and for sensitivity and specificity.

We also calculated risk scores from the cohorts under consideration using logistic regression models as a sensitivity analysis in order to obtain the impact of missing event time where outcome status were available. In this case, we modeled binary outcomes with the same predictors and methodology as of the above survival analysis. The risk score was then calculated using the methodology described above. The resulting risk score was also validated using the validation sample. Model calibration was conducted using Hosmer–Lemeshow goodness of fit test along calibration plots [57]. The

 $\lambda_{dementia}(t) = \lambda_{dementia,0}(t)\exp(\alpha * X + \alpha_1 * diabetes + \alpha_2 * MI + \alpha_3 * stroke)$ 

performance of the risk scores for identifying participants at risk of dementia and other outcomes was quantified by calculating the area under the curves (AUCs) and associated 95% CIs. For a given cut-off (quantile ranks) of the risk scores, we also compared relative odds ratios, sensitivity, and specificity. We validated each of these risk scores to include results for a model including only age, to examine whether the addition of other variables improved prediction.

### Results

### Description of the study dataset

Additional file 1: Table S2 presents covariates and outcome distribution in the study datasets. There was heterogeneity in sample size, profile of conditions/covariates, and outcomes across the datasets. Table 1 shows the distributions of outcomes and covariates in the model development (n=27,162) and validation (n=14,613) samples. The distribution of covariates in the model development and validation samples are similar. The mean age of study participants was 75.3 (6.8) years and 42% were male. Nearly a third of the study sample had a tertiary level of education. Median follow-up times (in years) for dementia, stroke, MI, and diabetes were 6.2, 7.0, 6.8, and 7.4, repectively. The major medical risk factors across cohorts were hypertension (47%), obesity (29.5%), hearing loss (15%), sleep problems (10%), TBI (9%), depression (9%), high total cholesterol (9%), and AF (6%). In terms of behavioral risk factors, 12% reported being a current smoker, 8% as heavy drinkers, and approximately 12% were engaged in moderate to high cognitive activities. A large proportion of covariates had missing data due to complete non-response of covariates. Nearly, 11%, 8%, 6%, and 4% of the pooled sample was diagnosed with incident dementia, stroke, MI, and diabetes, respectively. Around two thirds of the study participants died during follow-up. Among the cohorts, HRS ADAMS had only a few cases of incident diabetes (n=19), MI (n=4), and stroke (n=15), MAAS had lowest number of incident strokes recorded (n=3), and the Sydney Memory and Ageing Study had lowest number of incident diabetes cases (n=17). All the cohorts had ample number of dementia cases (Additional file 1: Table S2).

### **Development of DemNCD risk tools**

Table 2 reports the combined regression coefficients estimated in meta-analysis of parameters from the Fine and Gray sub-distribution model for dementia, stroke, MI, and diabetes, for males and females. In the dementia model, higher age, lower than tertiary education, insufficient physical activity, hearing loss, and stroke were significantly associated with increased dementia risk. For females, higher age, depression, loneliness, and stroke were significantly associated with increased dementia risk, whereas high cognitive activity, late-life obesity/ overweight, late-life moderate to high alcohol consumption, and sleep problems were significantly associated with a lower dementia risk.

In the stroke model, only hypertension was associated with increased risk for males. For females, hypertension, obesity, and high HDL were associated with decreased risk of stroke, whereas having had TBI and AF both were significantly associated with increased stroke risk.

In the MI model, previous history of diabetes was significantly associated with MI for both sexes. Among other medical covariates, hypertension, and AF, both were significantly associated with increased MI risk for females.

In the diabetes model, overweight and obesity were associated with increased risk among males. For females, diabetes risk increased for less than tertiary education, obesity, being a former smoker, and having had hypertension. However, higher age, moderate drinking, and having had high HDL decreased the risk of diabetes for females.

Despite most factors not being significantly associated with outcomes in the current analysis, we included all the covariates in the tool because risk assessment in practice is a key objective for the development of DemNCD tool. The approach aimed to provide comprehensive information of all the practical risk/protective factors to support clinical advice on risk reduction or enhancing protection. The points allocated to individual risk factors for the DemNCD tool associated with the regression coefficients are shown in Table 3.

### Validation of the DemNCD risk tools

Table 4 reports the Harrel C statistics of the DemNCD tool for predicting dementia, stroke, MI, and diabetes in the validation sample. The overall C-statistics (95% CI) for predicting dementia were 0.68 (0.65, 0.70) for males and 0.65 (0.63, 0.67) for females in the combined validation sample. On validating the model against each cohort separately, all the cohorts exhibited good prediction properties except for MAAS and FHS. This was because MAAS has only two female and four male dementia cases in the validation sample. In general, cohorts with longer exposure times, such as ARIC, CFAS I, CFAS II, and CHS, demonstrated better performance compared to other cohorts. The resulting wide confidence interval in the SLAS I dataset suggests significant population heterogeneity. Overall, prediction for dementia was better for females than males in all the validation cohorts except for FHS, MAAS, and MAS. CFAS II had the highest C-statistics for predicting dementia for females, where Harrel C (95% CI) was 0.75 (0.68, 0.82), whereas ARIC had the

### Table 1 Study characteristics of the validation and development sample

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§dney/Memory and Aging Study (MAS)676 (25)351 (21)361 (25)HHS- Aging, Demographics and Memory Study (HBS-ADAMS)57 (21)290 (21)Kaastrich Aging Study (MAAS)171 (21)174 (12)Kastrich Aging Study (MAAS)58 (23)439 (23)6 -60635 (23)439 (23)70 -74204 (66)387 (26)70 -74600 (22)334 (22)80 -84641 (167)445 (16)85 -892145 (79)1151 (79)90 +61 (25)60 (22)Age (mean, SD)M=753, SD=68M=753, SD=68KerMale11, 300 (1-0)60 (23)Secondary13, 101 (1-0)405 (13)90 +105 (15)485 (13)100 +13, 101 (1-0)485 (13)100 +13, 101 (1-0)485 (13)100 +13, 101 (1-0)485 (13)100 +13, 101 (1-0)25 (15)100 +140 (15)25 (15)101 +140 (15)25 (15)102 +11, 101 (1-0)102 (10)103 +13, 101 (1-0)13, 101 (1-0)104 +13, 101 (1-0)146 (13)105 +11, 101 (1-0)146 (13)104 +148 (153)146 (16)104 +148 (16)146 (16)105 +14, 101 (1-0)146 (10)104 +148 (16)146 (16)104 +148 (16)146 (16)105 +144 (16)146 (16)104 +148 (16)146 (16)104 + <t< td=""><td>The Singapore Longitudinal Ageing Studies (SLAS-I)</td><td>915 (3·4)</td><td>492 (3.4)</td></t<>	The Singapore Longitudinal Ageing Studies (SLAS-I)	915 (3·4)	492 (3.4)		
HS- Aging Demographics and Memory Study (HBS-ADAMS)SS7 (2 1)299 (2 1)Mattricht Aging Study (MAAS)17 (1 2)17 (1 2)Covariate:Covariate:Regroup (in years)Second (and and and and and and and and and and	Sydney Memory and Aging Study (MAS)	676 (2.5)	361 (2.5)		
Massticht Aging Study (MAAS)317 (12)174 (12)CovariatesAge group (in years)5565-696385 (23 S)3439 (23 S)70-747204 (26 S)3322 (29)80-844541 (167)245 (167)85-892145 (79)1151 (79)90+616 (25)361 (25)Age (mean, SD)M=753, SD=68M=753, SD=68SexMade11,300 (16)208 (139)5econdary11,300 (16)208 (139)5econdary13916 (512)746 (512)16rtary106 (512)486 (512)16rtary106 (512)486 (512)16rtary106 (512)208 (139)3sing010 (15)205 (15)Obesity101 (15)205 (15)Under weight235 (09)146 (10)Normal weight235 (09)156 (17)Normal weight235 (109)156 (17)Normal weight11,930 (12)295 (16)Obese295 (104)156 (17)Missing1481 (15)150 (16)Missing11,930 (12)696 (408)Former11,930 (12)696 (408)Missing11,930 (12)696 (406)Missing11,930 (12)696 (47)Missing11,930 (12)696 (47)Missing11,930 (12)696 (47)Missing11,930 (12)696 (47)Missing11,930 (12)696 (47)Missing11,930 (12)696 (47)Missing	HRS- Aging, Demographics and Memory Study (HRS-ADAMS)	557 (2.1)	299 (2.1)		
Covariates         Age group (in years)         3439 (235)         3439 (235)           65-69         6385 (235)         3439 (235)           70-74         7204 (265)         3875 (265)           75-79         6206 (228)         3324 (229)           80-84         451 (167)         151 (79)           85-89         2145 (79)         151 (79)           90+         681 (25)         361 (25)           84g (mean, 5D)         6079 (416)         6079 (416)           Page (man, 5D)         6051 (317)           Page	Maastricht Aging Study (MAAS)	317 (1·2)	174 (1.2)		
Age group (nyears)Age group (nyears)3852 (35)3430 (24)70-747204 (26)3875 (265)75-796206 (228)3440 (29)80-84641 (167)426 (167)80-84641 (167)616 (25)90+617 (25)617 (25)Age (mean SD)M=753 SD=68M=753 SD=68Neg (mage SD)M=753 SD=68<	Covariates				
65-696385 (23 S)3439 (23 S)70-74720 (26 S)367 (26 S)75-796206 (22 A)321 (22 9)80-844541 (167)245 (167)90 +620 (22 A)361 (25)90 +81 (25)361 (25)Age (mean, SD)M=753, SD=63M=753, SD=63Image colspan="2">In 300 (41 6)607 (416)SexMale1300 (41 6)607 (416)Secondary1301 (512)2038 (139)5 condary3916 (512)7485 (512)7 ertiary3916 (512)7485 (512)Normal weight31916 (512)7485 (512)Normal weight3190 (62)373 (62)Overweight5102 (188)203 (182)Coverweight3102 (188)205 (182)Normal weight3193 (152)363 (162)Obese950 (190)156 (107)Missing11,193 (412)696 (402)Current3118 (115)696 (402)Missing3118 (115)696 (402)Missing1200 (472)696 (2476)Missing3207 (472)696 (2476)Missing3207 (251)329 (246)Missing329 (121)183 (126)Sufficient329 (121)183 (126)Missing329 (251)359 (246)Missing329 (251)359 (246)Missing329 (251)359 (246)Missing120 (162)183 (126)Missing120 (162)183 (126)Missing3	Age group (in years)				
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75-796206 (2.8)3342 (2.9)80-84451 (167)2445 (7.6)80-84451 (57)245 (7.6)90+612 (2.5)361 (2.5)Age (mean, 5D)M=753, SD=68M=753, SD=68SerMale1.300 (14.6)0.79 (14.5)ElicationPrimary3672 (13.5)2038 (13.9)Secondary13.916 (51.2)4865 (33.3)Missing40(1.6)255 (15.9)Overweight2053 (19.9)Normal weight235 (0.9)146 (10.9)Normal weight5102 (18.8)2033 (16.2)Overweight5102 (18.8)2053 (18.2)Overweight5102 (18.8)2053 (18.2)Nating11.193 (1.2)964 (43.6)Singing11.193 (1.2)964 (43.6)Never11.993 (12.0)964 (43.6)Singing11.993 (12.0)964 (43.6)Missing11.993 (12.0)964 (43.6)Singing11.993 (12.0)964 (43.6)Missing19.903 (13.0)49.0116)Missing19.903 (13.0)49.0116)Missing19.903 (13.0)49.0116)Missing29.012119.602 (13.6)Singlicent29.012119.612,00Missing29.0121,0019.612,00Missing19.014 (12.7)19.612,00Missing19.014 (12.7)19.622,00Missing19.024 (12.1)19.612,00Missing19.024 (12.1)19.622,00Missing<	70–74	7204 (26·5)	3875 (26.5)		
80-844541 (167)2445 (167)85-892145 (7.9)1151 (7.9)90 +681 (2.5)681 (2.5)Age (mean, 5D)W=753, SD=68M=753, SD=68Secondary1,300 (41.6)M079 (41.6)EducationPrimary3672 (13.5)2038 (13.9)Secondary13.916 (51.2)7485 (51.2)Tetrary9164 (33.7)485 (33.3)Mising9104 (33.7)485 (33.3)ObesityUnder weight235 (0.9)146 (1.0)Normal weight235 (0.9)146 (1.0)Normal weight235 (0.9)146 (1.0)Normal weight235 (0.9)156 (10.7)Missing235 (10.9)156 (10.7)Missing11,93 (41.2)364 (40.8)Never11,930 (41.9)156 (10.7)Missing11,930 (41.9)156 (10.7)Missing12,900 (40.9)156 (10.7)Missing11,930 (41.9)156 (10.7)Missing12,900 (40.9)156 (10.7)Missing12,900 (40.9)156 (10.7)Missing12,900 (40.9)	75–79	6206 (22·8)	3342 (22.9)		
85-892145 (79)1151 (79)90+681 (25)681Age (mear, SD)687 (25)687Kale1,300 (41-6)6079 (41-6)Bolicitation2007 (13-5)6007 (13-6)Bolicitation3672 (13-5)6007 (13-6)Bolicitation3672 (13-5)7485 (51-2)Primary3672 (13-5)7485 (51-2)Secondary1964 (33.7)4865 (33.3)Missing1916 (1-2)7485 (51-2)Obesit1225 (1-5)Obesit1235 (0.9)146 (1.0)Normal weight3889 (16.2)2373 (16.2)Obesit235 (10-9)146 (1.0)Obesit235 (10-9)1565 (10-7)Missing1920 (148.3)205 (18-3)Obesit1930 (14.2)265 (10-7)Mever11,193 (41-2)5964 (40.8)Former11,193 (41-2)5964 (40.8)Missing11,193 (41-2)5964 (40.8)Missing11,193 (41-2)5964 (40.8)Missing11,193 (41-2)5964 (40.8)Missing11,193 (41-2)5964 (40.8)Missing11,200 (40-0)493 (3-1)Missing12,807 (47-2)5962 (47-6)Missing12,807 (47-2)5962 (47-6)Missing12,807 (47-2)5952 (47-6)Missing12,907 (41-2)5952 (47-6)Missing12,907 (41-2)1392 (42-6)Missing12,907 (41-2)1392 (24-6)Missing12,907 (41-2)1392	80-84	4541 (16·7)	2445 (16.7)		
90+         681(25)         361(25)           Age (mean, SD)         M=753, SD=68         M=753, SD=68           Sex         N         N           Male         1,300 (41-6)         0579 (41-6)           Education         N         N           Primary         3672 (13-5)         2038 (13-9)           Secondary         1,300 (61-2)         2038 (13-9)           Secondary         13,916 (51-2)         2038 (13-9)           Secondary         13,916 (51-2)         2038 (13-9)           Missing         0164 (33-7)         4865 (33-3)           Missing         2018 (23-2)         2018 (23-2)           Obesity         1014 (33-7)         2465 (33-3)           Under weight         235 (09-9)         146 (1-0)           Normal weight         235 (09-9)         146 (1-0)           Normal weight         2395 (10-9)         146 (1-0)           Obese         2955 (10-9)         1238 (12-5)           Never         11,193 (41-2)         5964 (40-8)           Former         2196 (24-0)         1396 (40-9)           Missing         290 (10-1)         1396 (40-1)         1396 (40-1)           Missing         200 (10-2)         1396 (20-1)         1396	85–89	2145 (7.9)	1151 (7.9)		
Age (mean, SD)M=753, SD=68M=753, SD=68SexMale1,300 (16)079 (16)Education1,300 (16)038 (13)Primary3672 (13.5)038 (13)Secondary13916 (51.2)7485 (51.2)Tertiary9164 (33.7)4865 (33.3)Missing9164 (33.7)4865 (33.3)Obesity140 (1.0)201.5Under weight235 (0.9)146 (1.0)Normal weight235 (0.9)146 (1.0)Normal weight235 (0.9)146 (1.0)Overweight140 (1.0)2373 (16.2)Overweight2373 (16.2)2373 (16.2)Overweight235 (0.9)146 (1.0)Missing295 (16.9)1565 (10.7)Missing195 (16.9)1565 (10.7)Missing195 (16.9)1565 (10.7)Missing195 (16.9)1565 (10.7)Missing195 (16.9)1565 (10.7)Missing196 (14.0)1565 (10.7)Missing196 (14.0)1565 (10.7)Missing196 (14.0)1565 (10.7)Missing196 (14.0)1565 (10.7)Missing196 (14.0)1565 (10.7)Missing196 (14.0)1690 (11.0)Missing196 (14.0)1690 (11.0)Missing198 (12.0)1690 (11.0)Missing198 (12.0)1690 (12.0)Missing198 (12.0)1690 (12.0)Missing198 (12.0)1690 (12.0)Missing198 (12.0)1690 (12.0)Missing </td <td>90+</td> <td>681 (2.5)</td> <td>361 (2.5)</td>	90+	681 (2.5)	361 (2.5)		
Sex         11,300 (41-6)         6079 (41-6)           Education            Primary         3672 (13-5)         2038 (13-9)           Secondary         13,916 (51-2)         4865 (33-3)           Tertiary         9164 (33-7)         4865 (33-3)           Missing         9164 (33-7)         4865 (33-3)           Missing         9164 (33-7)         4865 (33-3)           Missing         101 (5)         225 (1-5)           Obesity          225 (1-5)           Underweight         3089 (16-2)         235 (10-9)           Normal weight         2705 (18-5)         2705 (18-5)           Obese         102 (18-8)         2705 (18-5)           Obese         102 (18-8)         2705 (18-5)           Obese         102 (18-8)         2705 (18-5)           Soutig history         11,930 (1-2)         564 (40-8)           Missing         14,481 (53-3)         5964 (40-8)           Former         11,960 (44-0)         6466 (44-2)           Missing         1996 (13-0)         6400 (10-0)           Missing         1990 (14-0)         646 (44-2)           Missing         1990 (14-0)         646 (44-2)           Missing         199	Age (mean, SD)	M=75·3, SD=6·8	M = 75.3, $SD = 6.8$		
Male1,300 (1-6)6079 (1-6)Formary3672 (1-5)3038 (1-3)Secondary13.916 (1-5)7485 (5-1.2)Tertiary9164 (33.7)4856 (33.3)Missing9164 (33.7)252 (1-5)ObesityUnder weight235 (0.9)146 (1-0)Normal weight235 (0.9)146 (1-0)Normal weight012 (18.8)257 (18.8)Obese9102 (18.8)255 (10.9)Obese255 (10.9)156 (10.7)Missing11,930 (1-2)764 (40.8)Newer11,930 (1-2)824 (53.5)Former11,930 (1-2)646 (42.2)Current1196 (14.0)646 (42.2)Missing1193 (11.5)1690 (11.6)Missing12,807 (47.2)6362 (47.6)Missing12,807 (47.2)6362 (47.6)Missing12,807 (47.2)6362 (47.6)Missing12,807 (47.2)6362 (47.6)Missing12,807 (47.2)632 (24.6)Missing12,807 (47.2)6352 (24.6)Missing12,807 (47.2)6352 (24.6)Missing12,902 (14.6)1359 (24.6)Missing12,9	Sex				
Education         Note           Primary         3672 (13 5)         2038 (13 9)           Secondary         13,916 (51.2)         7485 (51.2)           Tetriary         9164 (33.7)         4865 (33.3)           Missing         410 (15)         225 (15)           Obesity         110 (15)         2373 (16.2)           Under weight         235 (0.9)         146 (1.0)           Normal weight         235 (0.9)         2373 (16.2)           Overweight         2373 (16.2)         2373 (16.2)           Overweight         5102 (18.8)         2705 (18.5)           Obese         1502 (19.8)         726 (18.5)           Obese         1502 (19.8)         726 (18.5)           Obese         1502 (19.8)         728 (53.5)           Obese         1502 (19.8)         728 (45.5)           Obese         11,93 (41.2)         5964 (40.8)           Former         11,930 (41.2)         5964 (40.8)           former         11,930 (41.2)         5964 (40.8)           Missing         910 (31.9)         430 (11.6)           Missing         1290 (11.6)         430 (11.6)           Missing         1280 (47.2)         6962 (47.6)           Missing <td< td=""><td>Male</td><td>11,300 (41.6)</td><td>6079 (41.6)</td></td<>	Male	11,300 (41.6)	6079 (41.6)		
Primary3672 (13.5)2038 (13.9)Secondary13,916 (51.2)7485 (51.2)Tertiary9164 (33.7)4865 (33.3)Missing410 (.5)225 (1.5)UUUUUUUUUUUUUUUUUUUUUUUUUUUUUUNever11,99 (14.2)DDDDUVNever11,99 (14.2)DDDDDDDDDDDDDDDD <td cols<="" td=""><td>Education</td><td></td><td></td></td>	<td>Education</td> <td></td> <td></td>	Education			
Seconday         13,916 (51-2)         7485 (51-2)           Tertiary         9164 (33.7)         4865 (33.3)           Missing         410 (1-5)         225 (1-5)           Obesity         2         250 (1-5)           Under weight         235 (0-9)         146 (1-0)           Normal weight         239 (16-2)         2373 (16-2)           Overweight         5102 (18.8)         2705 (18.5)           Obese         2955 (10-9)         1565 (10.7)           Missing         2481 (53.3)         7824 (53.5)           Normal weight         4481 (53.3)         7824 (53.5)           Never         11,960 (44-0)         6466 (44.2)           Former         11,960 (44-0)         6466 (44.2)           Gurrent         11,960 (44-0)         6466 (44.2)           Missing         891 (3.3)         893 (3.4)           Missing         891 (3.2)         6962 (47.6)           Missing         891 (3.2)         6962 (47.6)           Missing         502 (47.6)         200 (1.6)           Missing         502 (47.6)         200 (1.6)           Missing         502 (47.6)         200 (1.6)           Missing         502 (47.6)         3592 (42.6)           <	Primary	3672 (13.5)	2038 (13.9)		
Tertiary         9164 (337)         4865 (33.3)           Missing         410 (1-5)         225 (1-5)           Under weight         235 (0-9)         146 (1-0)           Normal weight         235 (0-9)         146 (1-0)           Normal weight         235 (0-9)         146 (1-0)           Overweight         5102 (188)         2705 (185)           Obese         2955 (10-9)         1565 (10-7)           Missing         11/93 (41-2)         5964 (40-8)           Former         11/93 (41-2)         5964 (40-8)           Current         3118 (11-5)         1690 (11-6)           Missing         11/94 (42-0)         6466 (42-2)           Missing         12807 (47-2)         6962 (47-6)           Missing         12807 (47-2)         6962 (47-6)           Missing         290 (19-0)         200 (19-0)           Pise attrivity         200 (19-0)         200 (19-0)           Missing         200 (20-0)         200 (20-0)         200 (20-0)           Sufficient         3294 (12-1)	Secondary	13,916 (51·2)	7485 (51.2)		
Missing         410 (1-5)         225 (1-5)           Under weight         235 (0-9)         146 (1-0)           Normal weight         235 (0-9)         237 (16-2)           Overweight         5102 (18.8)         2705 (18.5)           Obese         2955 (10-9)         1565 (10-7)           Missing         1481 (53.3)         705 (18.5)           Sweight         11,93 (41.2)         705 (18.5)           Never         11,193 (14.2)         705 (18.5)           Former         11,193 (14.2)         5964 (40.8)           Former         11,195 (14.4)         6466 (44.2)           Kuring Line         818 (13.5)         1690 (11-6)           Missing         819 (3.3)         493 (3.4)           Highbood pressure         2         2           Yes         12,807 (47.2)         6962 (47.6)           Missing         502 (14.7)         280 (1.9)           Highcent         3290 (12.1)         834 (12.6)           Missing         502 (24.7)         392 (24.6)           Missing         3294 (12.1)         1834 (12.6)           Sufficient         6327 (25.1)         392 (24.6)           Missing         12,041 (62.7)         392 (24.6)           <	Tertiary	9164 (33·7)	4865 (33.3)		
Obesity         235 (0.9)         146 (1.0)           Normal weight         235 (0.9)         2373 (16.2)           Overweight         5102 (18.8)         2705 (18.5)           Obese         2955 (10.9)         1565 (10.7)           Missing         14,481 (53.3)         7824 (53.5)           Smoking history         11,193 (41.2)         5964 (40.8)           Former         11,960 (44.0)         6466 (44.2)           Current         391 (3.3)         493 (3.4)           Missing         891 (3.3)         493 (3.4)           High bood pressure         12,807 (47.2)         6962 (47.6)           Missing         12,807 (47.2)         6962 (47.6)           Missing         12,807 (47.2)         6962 (47.6)           Missing         3294 (12.1)         1834 (12.6)           Sufficient         3294 (12.1)         1834 (12.6)           Missing         3294 (12.1)         1834 (12.6)           Sufficient         3294 (12.1)         1834 (12.6)           Missing         3294 (12.1)         1834 (12.6)           Sufficient         6827 (25.1)         3592 (24.6)           Missing         12,041 (62.7)         9187 (62.9)           Missing         3297 (87.9)         <	Missing	410 (1.5)	225 (1.5)		
norer weight         235 (0.9)         146 (1.0)           Normal weight         4389 (16.2)         2373 (16.2)           Overweight         5102 (18.8)         2705 (18.5)           Obese         2955 (10.9)         1565 (10.7)           Missing         14,481 (53.3)         7824 (53.5)           Swer         11,193 (41.2)         5964 (40.8)           Former         11,960 (44.0)         6466 (44.2)           Current         11,960 (44.0)         6466 (44.2)           Missing         891 (3.3)         493 (3.4)           Missing         891 (3.3)         493 (3.4)           Yes         12,807 (47.2)         6962 (47.6)           Missing         2020 (22.6)         392 (24.6)           Missing         12,807 (47.2)         6962 (47.6)           Missing         12,807 (47.2)         6962 (47.6)           Missing         12,807 (47.2)         5962 (43.6)           Missing         12,807 (47.2)         5962 (43.6)           Sufficient         6827 (25.1)         592 (24.6)           Missing         1294 (12.1)         1834 (12.6)           Sufficient         6827 (25.1)         592 (24.6)           Missing         17,041 (62.7)         1987 (62.9)	Obesity				
Normal weight         4389 (f6.2)         2373 (f6.2)           Overweight         5102 (18.8)         2705 (18.5)           Obese         2955 (10.9)         1565 (10.7)           Missing         14,481 (53.3)         7824 (53.5)           Sweight isory         11,193 (41.2)         5964 (40.8)           Former         11,960 (44.0)         6466 (44.2)           Current         3118 (11.5)         1690 (11.6)           Missing         891 (3.3)         493 (34)           Former         12,807 (47.2)         6962 (47.6)           Missing         6962 (47.6)         280 (1.9)           Ves         12,807 (47.2)         6962 (47.6)           Missing         2807 (47.2)         6962 (47.6)           Missing         540 (20.0)         280 (1.9)           Prysical activity         280 (1.9)         280 (1.9)           Less than sufficient         3294 (12.1)         1834 (12.6)           Sufficient         6827 (25.1)         3592 (24.6)           Missing         17,041 (62.7)         9187 (62.9)           Weight         70,411 (62.7)         1273 (87.)	Under weight	235 (0.9)	146 (1.0)		
Overweigh         5102 (18.8)         2705 (18.5)           Obese         2955 (10.9)         1565 (10.7)           Missing         14,481 (53.3)         7824 (53.5)           Smothing history         11,193 (41.2)         5964 (40.8)           Former         11,960 (44.0)         6466 (44.2)           Current         3118 (11.5)         1690 (11.6)           Missing         891 (3.3)         493 (3.4)           Hijb blood pressure         12,807 (47.2)         6962 (47.6)           Missing         12,807 (47.2)         6962 (47.6)           Missing         540 (2.0)         280 (1.9)           Prysical activity         2807 (47.2)         6962 (47.6)           Missing         540 (2.0)         280 (1.9)           Missing         540 (2.0)         280 (1.9)           Prysical activity         282 (12.1)         1834 (12.6)           Missing         1294 (12.1)         1834 (12.6)           Sufficient         6827 (25.1)         3592 (24.6)           Missing         17,041 (62.7)         9187 (62.9)           Hijb total cholesterol         Yes         2357 (87.)         1273 (87.)	Normal weight	4389 (16·2)	2373 (16·2)		
Obese         2955 (10.9)         1565 (10.7)           Missing         14,481 (53.3)         7824 (53.5)           Smoking history         11,193 (41.2)         5964 (40.8)           Former         11,960 (44.0)         6466 (44.2)           Current         3118 (11.5)         1690 (11.6)           Missing         891 (3.3)         493 (3.4)           High blood pressure         7         7           Yes         12,807 (47.2)         6962 (47.6)           Missing         280 (1.9)         280 (1.9)           Physical activity         280 (1.9)         280 (1.9)           Less than sufficient         3294 (12.1)         1834 (12.6)           Sufficient         6827 (25.1)         3592 (24.6)           Missing         17,041 (62.7)         9187 (62.9)           High total cholesterol         70,471 (62.7)         1837 (62.9)	Overweight	5102 (18.8)	2705 (18.5)		
Missing14,81 (53.3)7824 (53.5)Swoking history11,93 (41.2)5964 (40.8)Never11,960 (44.0)6466 (44.2)Former11,960 (44.0)6466 (44.2)Current3118 (11.5)1690 (11.6)Missing891 (3.3)493 (3.4)High blood pressureYes12,807 (47.2)6962 (47.6)Missing540 (20.0)280 (1.9)Physical activity280 (1.9)280 (1.9)Less than sufficient3294 (12.1)1834 (12.6)Sufficient6827 (25.1)3592 (24.6)Missing17,041 (62.7)9187 (62.9)High total cholesterolYes2357 (87.7)1273 (87.7)	Obese	2955 (10.9)	1565 (10.7)		
Smoking history         I11,193 (41-2)         5964 (40-8)           Former         11,960 (44-0)         6466 (44-2)           Current         3118 (11-5)         1690 (11-6)           Missing         891 (3-3)         493 (3-4)           High blood pressure         7         7           Yes         12,807 (47-2)         6962 (47-6)           Missing         540 (2-0)         280 (1-9)           Physical activity         280 (1-9)         280 (1-9)           Less than sufficient         3294 (12-1)         1834 (12-6)           Sufficient         6827 (25-1)         3592 (24-6)           Missing         17,041 (62-7)         9187 (62-9)           High total cholesterol         7         7	Missing	14,481 (53·3)	7824 (53.5)		
Never         11,193 (41-2)         5964 (40.8)           Former         11,960 (44.0)         6466 (44.2)           Current         3118 (11-5)         1690 (11-6)           Missing         891 (3.3)         493 (3.4)           High blood pressure         7         9           Yes         12,807 (47-2)         6962 (47-6)           Missing         540 (2.0)         280 (1-9)           Physical activity         280 (1-9)         280 (1-9)           Less than sufficient         3294 (12-1)         1834 (12-6)           Sufficient         6827 (25-1)         3592 (24-6)           Missing         17,041 (62-7)         9187 (62-9)           High total cholesterol         723 (8-7)         1273 (8-7)	Smoking history				
Former       11,960 (44.0)       6466 (44.2)         Current       3118 (11.5)       1690 (11.6)         Missing       891 (3.3)       493 (3.4)         High blood pressure         Yes       12,807 (47.2)       6962 (47.6)         Missing       540 (2.0)       280 (1.9)         Physical activity       280 (1.9)       280 (1.9)         Less than sufficient       3294 (12.1)       1834 (12.6)         Sufficient       6827 (25.1)       3592 (24.6)         Missing       17,041 (62.7)       9187 (62.9)         High total cholesterol       17,041 (62.7)       1834 (12.6)         Kes       1273 (8.7)       1273 (8.7)	Never	11,193 (41·2)	5964 (40.8)		
Current       3118 (11-5)       1690 (11-6)         Missing       891 (3-3)       493 (3-4)         High blood pressure       12,807 (47-2)       6962 (47-6)         Missing       540 (2-0)       280 (1-9)         Physical activity       280 (1-9)       280 (1-9)         Less than sufficient       3294 (12-1)       1834 (12-6)         Sufficient       6827 (25-1)       3592 (24-6)         Missing       17,041 (62-7)       9187 (62-9)         High total cholesterol       1273 (8-7)	Former	11,960 (44.0)	6466 (44·2)		
Missing         891 (3·3)         493 (3·4)           High blood pressure             Yes         12,807 (47·2)         6962 (47·6)           Missing         540 (2·0)         280 (1·9)           Physical activity         280 (1·9)            Less than sufficient         3294 (12·1)         1834 (12·6)           Sufficient         6827 (25·1)         3592 (24·6)           Missing         17,041 (62·7)         9187 (62·9)           High total cholesterol         Yes         2357 (8·7)         1273 (8·7)	Current	3118 (11.5)	1690 (11.6)		
High blood pressure       12,807 (47.2)       6962 (47.6)         Yes       12,807 (47.2)       6962 (47.6)         Missing       540 (2.0)       280 (1.9)         Physical activity       280 (1.9)       100         Less than sufficient       3294 (12.1)       1834 (12.6)         Sufficient       6827 (25.1)       3592 (24.6)         Missing       17,041 (62.7)       9187 (62.9)         High total cholesterol       7       1273 (8.7)	Missing	891 (3.3)	493 (3.4)		
Yes     12,807 (47-2)     6962 (47-6)       Missing     540 (2-0)     280 (1-9)       Physical activity     12,807 (47-2)     1800 (1-9)       Less than sufficient     3294 (12-1)     1834 (12-6)       Sufficient     3294 (12-1)     1834 (12-6)       Sufficient     6827 (25-1)     3592 (24-6)       Missing     17,041 (62-7)     9187 (62-9)       High total cholesterol     2357 (8-7)     1273 (8-7)	High blood pressure				
Missing         540 (2-0)         280 (1-9)           Physical activity         2540 (2-0)         280 (1-9)           Less than sufficient         3294 (12-1)         1834 (12-6)           Sufficient         6827 (25-1)         3592 (24-6)           Missing         17,041 (62-7)         9187 (62-9)           High total cholesterol         2357 (8-7)         1273 (8-7)	Yes	12,807 (47·2)	6962 (47.6)		
Physical activity         3294 (12·1)         1834 (12·6)           Less than sufficient         3294 (12·1)         1834 (12·6)           Sufficient         6827 (25·1)         3592 (24·6)           Missing         17,041 (62·7)         9187 (62·9)           High total cholesterol         2357 (8·7)         1273 (8·7)	Missing	540 (2.0)	280 (1.9)		
Less than sufficient         3294 (12·1)         1834 (12·6)           Sufficient         6827 (25·1)         3592 (24·6)           Missing         17,041 (62·7)         9187 (62·9)           High total cholesterol         2357 (8·7)         1273 (8·7)	Physical activity				
Sufficient         6827 (25·1)         3592 (24·6)           Missing         17,041 (62·7)         9187 (62·9)           High total cholesterol         2357 (8·7)         1273 (8·7)	Less than sufficient	3294 (12.1)	1834 (12.6)		
Missing     17,041 (62-7)     9187 (62-9)       High total cholesterol     2357 (8-7)     1273 (8-7)	Sufficient	6827 (25.1)	3592 (24.6)		
High total cholesterol         2357 (8-7)         1273 (8-7)	Missing	17,041 (62.7)	9187 (62.9)		
Yes 2357 (8-7) 1273 (8-7)	High total cholesterol	· · · /			
	- Yes	2357 (8.7)	1273 (8.7)		

### Table 1 (continued)

	Combined sample				
	Development sample n=27,162 (%)	Validation sample n = 14,613 (%)			
Missing	15,154 (55-8)	8184 (56·0)			
High-density lipoprotein					
High	6183 (22·8)	3311 (22.7)			
Missing	17,886 (65·8)	9634 (65·9)			
Low-density lipoprotein					
High	1121 (4-1)	615 (4·2)			
Missing	17,710 (65·2)	9535 (65·3)			
Traumatic brain injury					
Yes	2502 (9·2)	1367 (9.4)			
Missing	7271 (26.8)	3942 (27.0)			
Depression					
Yes	2410 (8·9)	1325 (9.1)			
Missing	2418 (8·9)	1305 (8.9)			
Alcohol consumption					
Abstain	7537 (27.7)	3995 (27.3)			
Moderate	6769 (24.9)	3667 (25.1)			
Heavy	2054 (7.6)	1161 (7.9)			
Missing	10,802 (39·8)	5790 (39·6)			
Fruits and vegetable					
≥5 servings/week	8830 (32.5)	4707 (32-2)			
Missing	16,736 (61.6)	9023 (61.7)			
Fish intake					
≥2 servings/week	5861 (21.6)	3144 (21.5)			
Missing	14,380 (52·9)	7813 (53.5)			
Cognitive engagement					
Low	5138 (18·9)	2809 (19·2)			
Moderate	1662 (6·1)	878 (6)			
High	1508 (5.6)	771 (5·3)			
Missing	18,854 (69·4)	10,155 (69.5)			
Loneliness					
Yes	875 (3.2)	483 (3·3)			
Missing	14,075 (51·8)	7573 (51.8)			
Atrial fibrillation					
Yes	1662 (6·1)	897 (6.1)			
Missing	16,467 (60.6)	8856 (60.6)			
Hearing loss					
Yes	4092 (15·1)	2130 (14.6)			
Missing	4267 (15-7)	2298 (15-7)			
Sleep problem	0705 (40.0)	4504 (40.0)			
Yes	2795 (10.3)	1504 (10.3)			
Missing	13,154 (48-4)	/086 (48.5)			
Outcomes					
Diabetes	1145 (4.5)	501 (1.0)			
Incident	1145 (4-2)	591 (4.0)			
Prevalent	3/3/ (13.8)	2029 (13.9)			
Missing	322 (1.2)	172 (1.2)			

### Table 1 (continued)

	Combined sample				
	Development sample $n = 27,162$ (%)	Validation sample n = 14,613 (%)			
Stroke					
Incident	2146 (7·9)	1083 (7.4)			
Prevalent	1720 (6·3)	955 (6.5)			
Missing	273 (1.0)	161 (1.1)			
МІ					
Incident	1701 (6·3)	928 (6·4)			
Prevalent	2509 (9·2)	1389 (9.5)			
Missing	357 (1·3)	191 (1.3)			
Dementia					
Incident	2931 (10.8)	1575 (10.8)			
Prevalent	928 (3·4)	480 (3.3)			
Missing	2623 (9.7)	1429 (9.8)			
Death	18,127 (66·7)	9820 (67-2)			

Definition of covariates and outcome are provided in Additional file 1: Table S1 and Table S3, respectively

highest C-statistics for males (C-statistics, 0.72 95% CI 0.68, 0.76).

Compared with dementia, the DemNCD resulted in similar C-statistics for MI and diabetes, however, was somewhat lower for stroke. The overall C-statistics (95% CI) for predicting stroke were similar for both males 0.58 (0.54, 0.61) and females 0.55 (0.52, 0.57) in the combined sample. All the cohort components of the validation sample provided similar C-statistics. For prediction of MI using the DemNCD tool, the overall C-statistics (95% CI) were also similar for males 0.65 (0.61, 0.68) and females 0.65 (0.62, 0.68) in the combined sample. For prediction of diabetes using the DemNCD tool, the overall C-statistics (95% CI) were 0.68 (0.64, 0.72) and 0.61 (0.57, 0.65) for males and females, respectively, in the combined sample. Among the individual cohorts in the validation sample, all the cohorts provided similar C-statistics, except for HRS-ADAMS and MAS for males' sample. This was because low number of incident diabetes were available in the validation sample for these cohorts (two incident diabetes cases in males for both HRS-ADAMS and MAS).

## Comparison of sensitivity, specificity, and cutoff points of DemNCD

Table 5 reports the quantile cut-offs, sub-distribution hazards ratios, sensitivity, and specificity for predicting dementia, stroke, MI, and diabetes. The final risk scores for predicting the four outcomes were similar for the model development and validation cohorts and sexes. The final score ranges from -34 to 72 for dementia, -24 to 32 for stroke, -7 to 47 for MI, and -42 to 45

for diabetes. Overall, the sub-distribution hazards (sHR) increased for higher quantile-cut-offs for DemNCD risk for all outcomes. The model and validation datasets provided similar sensitivity and specificity for a given cut-off.

## Sensitivity analysis: DemNCD risk tool development and validation using logistic regression (DemNCD-LR)

Additional file 1: Table S4 reports the combined regression coefficients estimated by meta-analysis of logistic regression model parameters for dementia, stroke, MI, and diabetes for both males and females. In general, the regression coefficients from logistic regression models were comparable to the regression coefficients of Fine and Gray sub-distribution models. The corresponding points for the DemNCD-LR tools are given in Additional file 1: Table S5.

Figure 1 and Additional file 1: Table S6 show the predictive accuracy of the DemNCD-LR risk tools. We obtained very similar predictive accuracy in the Dem-NCD-LR for males and females for all four outcomes. The AUC (95% CI) for dementia were 0.70 (0.68, 0.72) and 0.66 (0.64, 0.68), for stroke 0.57 (0.54, 0.60) and 0.61 (0.59, 0.64), for MI 0.67 (0.65, 0.70) and 0.65 (0.62, 0.68), and for diabetes 0.69 (0.65, 0.72) and 0.63 (0.59, 0.66) for males and females, respectively. The Hosmer–Lemeshow goodness of fit (Additional file 1: Table S7) and the calibration plots (Additional file 1: Figs. S2-S5) show that the DemNCD-LR provides systematic overestimation of risks in males, but relatively poor calibration for stroke, MI, and diabetes in females.

Finally, Additional file 1: Table S8 reports sensitivity, specificity, and OR corresponding to the quantiles

Table 2 Sub-distribution hazar	ds regression coefficients for individual risk/protective factors ( $\beta$ , 95% Cl) obtained through r	meta-
analysis following Fine and Gray	sub-distribution hazards model	

Covariates Dementia		Stroke		МІ		diabetes		
	Male	Female	Male	Female	Male	Female	Male	Female
Age								
65–69	- 0·38 (- 0·71, - 0·05)	−0·47 (−0·77,−0·16)	-0.12 (-0.34, 0.11)	-0.00 (-0.22, 0.21)	0·14 (- 0·09, 0·36)	0·10 (- 0·13, 0·34)	0·24 (−0·12, 0·61)	0.15 (-0.08, 0.38)
70-74	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
75–79	0·54 (0·33, 0·75)	0∙39 (0∙14, 0∙64)	0·08 (– 0·15, 0·31)	0∙20 (0∙02, 0∙38)	0·17 (-0·07, 0·41)	0·14 (−0·08, 0·35)	0·06 (−0·24, 0·36)	- 0·27 (- 0·53, - 0·01)
80–84	0·77 (0·44, 1·10)	0·92 (0·49, 1·35)	0·22 (- 0·03, 0·47)	0.09 (-0.31, 0.50)	0·14(−0·33, 0·61)	0·07 (-0·20, 0·34)	-0·38 (-0·93, 0·17)	- 0·47 (- 0·82, - 0·12)
85–89	1·27 (0·94, 1·60)	1∙18 (0∙52, 1∙85)	−0·25 (−0·72, 0·23)	−0·00(−0·50, 0·49)	- 0·09 (- 0·98, 0·80)	-0.02 (-0.43, 0.39)	- 0·37 (- 1·15, 0·40)	- 1·03 (- 1·69, - 0·37)
90+	2·45 (1·52, 3·39)	1·60 (0·92, 2·28)	-0·31 (-1·63, 1·01)	−0·74 (−1·76, 0·29)	0·43 (0·62, 1·49)	-0.08 (-1.20, 1.05)	*	*
Education								
Less than second- ary	0·35 (0·10, 0·60)	0.14 (-0.06, 0.33)	-0.03 (-0.29, 0.24)	0.18 (-0.02, 0.39)	0·00 (−0·26, 0·26)	0·20 (−0·17, 0·57)	0·05 (−0·32, 0·43	0•49 (0•18, 0•79)
Upper secondary	0·22 (0·02, 0·42)	0.10 (-0.05, 0.25)	0·05 (−0·16, 0·27)	0.08 (-0.11, 0.27)	- 0·08 (- 0·45, 0·29)	0·27 (0·06, 0·48)	0·05 (−0·25, 0·34)	0·26 (0·00, 0·51)
Tertiary	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Obesity								
Under- weight	0.55 (-0.36, 1.47)	0.09 (-0.39, 0.56)	-0.03 (-1.15, 1.09)	−0·28 (−0·84, 0·29)	0·58 (−0·53, 1·69)	-0.07 (-0.75,0.61)	*	−0·51 (−1·68, 0·67)
Normal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Over- weight	−0·01 (−0·21, 0·20)	−0·15 (−0·29, −0·00)	0·11 (−0·11, 0·32)	−0·09 (−0·25, 0·07)	0∙24 (0∙03, 0∙45)	0·16 (−0·05, 0·36)	0·59 (0·19, 0·99)	0.19 (-0.06, 0.44)
Obese	0.06 (-0.22, 0.34)	-0·32 (-0·52, -0·13)	0·04 (- 0·26, 0·33)	-0·20 (-0·40,-0·01)	0·19 (-0·24, 0·63)	0·22 (−0·18, 0·62)	0·98 (0·59, 1·37)	0.89 (0.55, 1.24)
Alcohol cons	umption							
Low	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	-0.23 (-0.45,-0.00)	-0·28 (-0·46, -0·10)	0·12 (−0·12, 0·35)	-0·04 (-0·21 0·13)	0·09 (- 0·12, 0·30)	-0.00 (-0.27, 0.27)	-0·19 (-0·47, 0·08)	-0·29 (-0·56,-0·03)
High	−0·06 (−0·38, 0·26)	- 0·47 (- 0·89, - 0·05)	0·15 (−0·18, 0·48)	−0·15 (−0·56, 0·26)	0·02 (- 0·32, 0·37)	0·46 (−0·89, 1·80)	−0·05 (−0·49, 0·39)	−0.66 (−1.41, 0.09)
Smoking								
Non- smoker	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Current smoker	−0·14 (−0·31, 0·04)	−0·12 (−0·28, 0·03)	-0.07 (-0.31,0.16)	−0·12 (−0·27, 0·02)	0·14 (−0·06, 0·33)	0·07 (−0·10, 0·24)	0·05 (−0·20, 0·31)	0.13 (-0.07, 0.34)
Former smoker	−0·02 (−0·32, 0·29)	0.21 (-0.04, 0.45)	−0·13 (−0·57, 0·31)	0.14 (-0.20, 0.48)	-0.10 (-0.69, 0.49)	−0·10 (−0·40, 0·20)	0·14 (−0·29, 0·57)	0·38 (0·08, 0·69)
Hyperten- sion (yes)	−0·01 (−0·18, 0·17)	−0·05 (−0·21, 0·11)	0∙19 (0∙01, 0∙36)	0∙26 (0∙06, 0∙46)	0·07 (−0·11, 0·25)	0·19 (0·02, 0·36)	0·19 (−0·05, 0·42)	<b>0·28 (0·09, 0·48</b> )
Cholesterol (high)	0.19 (-0.27, 0.66)	0.24 (-0.01, 0.48)	0·28 (−0·11, 0·66)	−0·11 (−0·36, 0·15)	−0·14 (−0·58, 0·30)	0·04 (-0·26, 0·34)	0·32 (- 0·28, 0·92)	−0·23 (−0·60, 0·14)
High HDL	0.13 (-0.10, 0.36)	−0·13 (−0·30, 0·05)	-0.18 (-0.38, 0.02)	−0·16 (−0·31,−0·00)	- 0·05 (- 0·25, 0·15)	-0.12 (-0.30, 0.06)	−0·22 (−0·50, 0·07)	-0.29 (-0.52,-0.06)
High LDL	0.08 (-0.49, 0.65)	−0·26 (−0·62, 0·09)	0·07 (−0·64, 0·78)	0.37 (-0.22, 0.96)	0·34 (- 0·11, 0·79)	0·07 (-0·29, 0·43)	−0·39 (−1·04, 0·25)	−0·14 (−0·58, 0·29)
Depression (yes)	-0.09 (-0.41, 0.23)	0∙21 (0∙00, 0∙42)	0·33 (-0·11, 0·77)	0.00 (-0.23, 0.23)	0·23 (−0·14, 0·60)	-0.03 (-0.27, 0.22)	-0.07 (-0.53, 0.39)	0.17 (-0.10, 0.44)
Fish serve	0.09 (-0.11, 0.30)	0.00 (-0.15, 0.15)	-0.02 (-0.21,0.17)	0.02 (-0.13, 0.18)	-0.03 (-0.22, 0.16)	-0.06 (-0.24, 0.12)	0·02 (−0·25, 0·29)	0.07 (-0.16, 0.30)

### Table 2 (continued)

Covariates	ovariates Dementia		Stroke	Stroke			diabetes		
	Male	Female	Male	Female	Male	Female	Male	Female	
Fruits and vegetable	-0.02 (-0.38, 0.34)	−0·20 (−0·55, 0·14)	-0·30 (-0·76, 0·17)	−0·20 (−0·65, 0·26)	0·55 (0·08, 1·17)	0·11 (-0·45, 0·66)	0·03 (-0·58, 0·64)	0.22 (-0.51, 0.95)	
TBI (yes)	0.00 (-0.22, 0.22)	−0·03 (−0·26, 0·19)	0·09 (−0·20, 0·38)	0·32 (0·03, 0·61)	0·04 (-0·31, 0·40)	- 0·31 (- 0·77, 0·14)	-0.02 (-0.48, 0.43)	0.21 (-0.18, 0.61)	
Loneliness (yes)	0.22 (-0.26, 0.70)	0·44 (0·10, 0·44)	0·26 (- 0·21, 0·73)	-0.01 (-0.31, 0.28)	0·24 (- 0·23, 0·71)	0·03(- 0·33, 0·38)	-0.09 (-0.86, 0.69)	0.14 (-0.27, 0.55)	
Insufficient physical activity	0·28 (0·06, 0·49)	0.08 (-0.09, 0.24)	-0.02 (-0.41, 0.37)	−0·03 (−0·26, 0·20)	0·07 (−0·44, 0·59)	0·12 (−0·06, 0·30)	-0.11 (-0.42, 0.19)	-0·03 (-0·31, 0·24)	
Cognitive ac	tivity								
Low	Ref	Ref	Not included		Not included		Not included		
Moderate	0.06 (-0.48, 0.59)	−0·03 (−0·33, 0·27)							
High	- 0·63 (- 1·35, 0·09)	- 0·40 (- 0·80, - 0·01)							
Atrial fibril- lation	0.14 (-0.10, 0.38)	0.12 (-0.08, 0.32)	0·25 (0·01, 0·52)	0·34 (0·09, 0·59)	0·37 (0·31, 1·06)	0·45 (0·10, 0·80)	- 0·02 (- 0·40, 0·36)	0.01 (-0.33, 0.36)	
Sleep prob- lem	0.00 (-0.47, 0.47)	- 0·23 (- 0·43, - 0·03)	0·26 (−0·14, 0·65)	−0·10 (−0·28, 0·09)	0·50 (−0·26, 1·25)	0·13 (- 0·09, 0·34)	0·14 (−0·29, 0·57)	−0·12 (−0·40, 0·16)	
Hearing loss	0·22 (0·03, 0·41)	−0.00 (−0.17, 0.17)	0·01 (0·23, 0·26)	0.12 (-0.09, 0.34)	-0·12 (-0·46, 0·22)	0·17 (−0·10, 0·44)	0·04 (−0·30, 0·38)	0.21 (-0.12, 0.53)	
Diabetes	0.02 (-0.17, 0.20)	0.04 (-0.11, 0.19)	0·15 (−0·07, 0·36)	0.14 (-0.03, 0.31)	0·23 (0·04, 0·43)	0∙32 (0•15, 0•50)	Not included		
Stroke	0·65 (0·48, 0·83)	0·41 (0·24, 0·59)	Not included		0·13 (- 0·08, 0·34)	0·35 (−0·14, 0·83)			
МІ	-0·21 (-0·52, 0·09)	−0·08 (−0·26, 0·11)	0·13 (- 0·05, 0·32)	0.22 (-0.03, 0.40)	Not included				

cut-offs for DemNCD-LR risk scores for males and females. Similar to the DemNCD risk tools, the final risk scores for predicting the four outcomes were similar for the model development and validation cohorts.

## Comparison of the full DemNCD/DemNCD-LR versus age only model

We also examined whether the DemNCD/DemNCD-LR models with all the risk/protective factors provided better predictive ability compared with the age only model, as previous dementia risk tools suggest that an age alone model for dementia provides similar predictive ability as a full model [9]. Similar to the previous tools, the age only model provided similar C-statistics as the full model (see Additional file 1: Table S9). However, for other outcomes, adding risk factors to age improved the predictive ability.

### Discussion

To our knowledge, DemNCD is the first attempt to develop a risk tool based on a common set of predictors for dementia, stroke, MI, and diabetes that is suitable for use in routine clinical practice. The DemNCD focuses on relatively short term prediction and hence can be used as an educational and motivational tool as well as to target the interventions for those most at risk. Our results demonstrate that the proposed risk tools (Dem-NCD/DemNCD-LR) provide good prediction properties for dementia, MI, diabetes, and strokes especially for older adults aged 65 and above. For estimating dementia risk, comparable C-statistics were obtained using Dem-NCD and DemNCD-LR, as are found with existing risk tools for dementia (CogDrisk, ANU-ADRI, CAIDE, and LIBRA [9, 11]). For predicting stroke, we obtained lower C-statistics compared to dementia prediction, but comparable C-statistics estimate was obtained to those of existing risk scores such as the Framingham stroke risk score [12], the Stroke Riskometer [13], and the Qstroke for older adults [58]. In addition, similar C-statistics for predicting stroke and cardiovascular disease among older adults have been reported elsewhere [58-60].

For estimating risk of MI, our DemNCD/DemNCD-LR risk tools provide comparable AUC (95% CI) estimates to the TMTI (AUC ranges from 0.65 to 0.68) [15], the INHEART (AUC (95% CI) for men > 55 years and female > 65 years is 0.67 (0.65, 0.69)) [17], and the Essen risk score (AUC 0.64 95% CI (0.57–0.71) [16].

MaleFemaleMaleFemaleMaleFemaleMaleFemaleAge65:69-8-9-20325370-74000000075.791182431-580-8415144231-580-842524-50-20-7-2191+4932-1159-21591+493-1103110Upper secondary73-1404110Upper secondary73-1-612-1*10Upper secondary73-1-612-1*1010Underweight0000000000Overreight0-32-2531244Obesc-1-4420181442018Actoric consumption-5-62-120-442018Moderate-5-62-12312451-6-5-6312133-7331246-6-5-613	Covariates	Dementia		Stroke		MI		Diabetes	
Age        8         -9         -7         0         3         2         5         3           07-74         0 <td< th=""><th></th><th>Male</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th><th>Male</th><th>Female</th></td<>		Male	Female	Male	Female	Male	Female	Male	Female
65-69         -8         -9         -2         0         3         2         5         3           70.74         0 <t< td=""><td>Age</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Age								
76-74000000000075 79118231-8-985-802524-6-159-2**80+423-7-213-7-2190+42524-6-159-2**80+70-6-159-2***100-00000000100000000000100 <t< td=""><td>65-69</td><td>-8</td><td>-9</td><td>-2</td><td>0</td><td>3</td><td>2</td><td>5</td><td>3</td></t<>	65-69	-8	-9	-2	0	3	2	5	3
75-7911824331 $-5$ $80-84$ 15144231 $-8$ $-9$ $95+9$ 2524 $-5$ 0 $-2$ 0 $-8$ $-9$ $90+$ 4932 $-6$ $-15$ 9 $-2$ ***ElucationLess has secondary4212 $-2$ $2$ $1$ $0$ $0$ Obesity112 $-1$ $6$ $2$ $-2$ $5$ $1$ $5$ $-10$ Obesity11 $2$ $-1$ $-6$ $12$ $-1$ $*$ $-10$ Obesity $11$ $2$ $-1$ $-6$ $12$ $-1$ $*$ $-10$ Obesity $11$ $2$ $-1$ $-6$ $12$ $-1$ $*$ $-10$ Obesity $11$ $2$ $-1$ $-6$ $12$ $-1$ $*$ $-10$ Obesity $-1$ $-6$ $12$ $-1$ $12$ $12$ $12$ $12$ $12$ $12$ $12$ Obesity $-1$ $-6$ $2$ $2$ $2$ $12$	70–74	0	0	0	0	0	0	0	0
B0-84         15         14         4         2         3         1         -8         -9           B5-80         25         24         -5         0         -2         0         -7         -21           B0-90         25         24         -6         -15         0         -2         2         -7         -21           Education	75-79	11	8	2	4	3	3	1	-5
B3-B9         P3         P4         -5         0         -2         0         -7         -21           90+         4         32         -6         -15         9         -2         *         *           Education         E         E         E         E         E         10         10           Upper secondary         4         2         1         2         -2         5         1         5           Printary         0         0         0         0         0         0         0         0         0           Obesity         I         2         -1         -6         12         -1         *         -10           Nermal weight         0	80-84	15	14	4	2	3	1	-8	-9
90+4932-64-159-2***EtausationLess than secondary73-1010410Upper secondary7000000000Tertary00000000000Obesity112-11-612-11*-10*-10Norral weight000	85-89	25	24	-5	0	-2	0	-7	-21
Education         Product of the secondary         Product of the second	90+	49	32	-6	-15	9	-2	*	*
Less marsecondary         7         3         -1         4         0         4         1         10           Upper secondary         4         2         1         2         -2         5         1         5           Tertiary         0         0         0         0         0         0         0         0           Obesity          -         -         6         12         -1         *         -10           Normal weight         0 <td>Education</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Education								
Dyper secondary         4         2         1         2         -2         5         1         5           Tertiary         0         0         0         0         0         0         0         0         0           Obesity         -         -         -         -         -         1         *         -         0           Mormal weight         0	less than secondary	7	3	-1	4	0	4	1	10
Tertiary         0         0         0         0         0         0         0         0         0           Jentary         0         0         0         0         0         0         0         0         0           Obesity           -6         12         -1         *         -10           Morral weight         0         0         0         0         0         0         0         0           Obese         -1         -3         2         -2         5         3         12         4           Alcohol consumption	Upper secondary	4	2	1	2	-2	5	1	5
Check         C <thc< th="">         C         <thc< th=""> <thc< th=""></thc<></thc<></thc<>	Tertiary	0	0	0	0	0	0	0	0
Lunderweight         11         2 $-1$ $-6$ $12$ $-1$ $*$ $-10$ Normal weight         0         0         0         0         0         0         0         0         0           Otherweight         0 $-3$ $2$ $-2$ $5$ $3$ $12$ $4$ Obese $-1$ $-6$ $12$ $-2$ $5$ $3$ $12$ $4$ Obese $-1$ $-6$ $2$ $-1$ $2$ $0$ $0$ $0$ Acchol consumption $-1$ $-9$ $3$ $-1$ $2$ $0$ $-1$ $-6$ High $-1$ $-9$ $3$ $-1$ $2$ $0$ $-1$ $-3$ Smoking $-3$ $-2$ $-1$ $2$ $3$ $1$ $4$ $4$ $6$ Former smoker $0$ $4$ $-3$ $-2$ $-2$ $3$ $-2$ $-3$ Papertension (yes) <th< td=""><td>Obesity</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th<>	Obesity								
Normal weight         0         a         1         a         1         a         1         a         1         a         1         a         1         a         1         a         1         0	Underweight	11	2	-1	-6	12	- 1	*	- 10
International form         0         -3         2         -2         5         3         12         4           Obese         -1         -6         1         -4         4         4         20         18           Alcoha         T         -6         1         -4         4         4         20         18           Alcoha         T         -6         1         -4         4         4         20         18           Alcoha         -5         -6         2         -11         2         0         -4         -6           High         -1         -9         3         -3         0         9         -1         -13           Smoking         -1         -2         1         2         0         0         0         0         0         0         0         0         1         3         3         -2         3         1         1         3         1         3         4         6         6         6         -2         -2         3         8         Hyperbasion (yes)         0         -1         -2         -4         -6         1         1         -2         -2         -2<	Normal weight	0	0	0	0	0	0	0	0
Obese         -1         -6         1         -4         4         4         20         18           Alcohol consumption         -5         -6         0         0         0         0         0         0         0         0         0           Moderate         -5         -6         2         -1         2         0         -4         6           High         -1         -6         2         -1         2         0         -4         6           High         -1         -6         2         -1         2         0         -4         -6           Smoking         -5         -6         2         -1         2         0         0         -1         -6           Mon-smoker         0         0         0         0         0         0         0         0         0           Current smoker         0         4         -3         3         -2         -2         3         8         8           Hypertension(ves)         0         -1         4         5         1         4         6           Cholesterol (high)         4         5         1         7 <t< td=""><td>Overweight</td><td>0</td><td>- 3</td><td>2</td><td>-2</td><td>5</td><td>3</td><td>12</td><td>4</td></t<>	Overweight	0	- 3	2	-2	5	3	12	4
Actional consumption         Actional consumption         Actional consumption         Actional consumption           Low         0         0         0         0         0         0         0         0           Moderate         -5         -6         2         -1         2         0         -4         -6           High         -1         -6         2         -1         2         0         -4         -6           Smoking         -1         -2         3         0         9         -1         3           Current smoker         -3         -2         -1         -2         3         1         1         3           Former smoker         0         0         -1         -2         3         1         4         6           Collectore(Integration (yes)         0         -1         4         5         6         -2         -3         1         8         -5           High LDL         2         -5         1         7         7         1         -8         -3           Depression (yes)         -2         4         7         0         5         1         -2         3           Fi	Obese	-1	-6	-	-4	4	4	20	18
Low         0         0         0         0         0         0         0         0         0         0         0           Moderate         -5         -6         2         -1         2         0         -4         -6           High         -1         -9         3         -3         0         9         -1         -13           Smokig          -         -3         0         9         -1         -13           Current smoker         -3         -2         -1         -2         3         1         1         3           Constroker         -3         -2         -1         -2         3         1         1         3         3           Corrent smoker         0         4         -3         3         -2         -2         3         8           Hypertension (ves)         0         -1         4         4         6         -5           High HDL         3         -3         -4         -2         -3         -1         -6         -5           High HDL         3         -3         1         7         7         1         -2         3         -2<	Alcohol consumption		0		·	·		20	10
Moderate Moderate-5-62-120-4-6High-1-93-309-1-13Smoking00009-1-13Smoking0000000000Current smoker0000000000Current smoker04-33-2-23113Former smoker04-33-2-2316-5High HDL3-3-4-3-1-18-3Depression (yes)0-11771-8-3Depression (yes)-24705-1-13Fish serve200121444Furths and vegetable0-4-6-1-1-133Fish serve20-121-1444Fulls and vegetable0-4-6-1-11214Fulls and vegetable0-120-112331Ibig Alerati High1350112333Fulls and veget	low	0	0	0	0	0	0	0	0
High High-1-93-300-1-13SmokingNon-smoker000000000Current smoker-3-2-1-23113Former smoker04-33-2-238Hypertension (yes)0-145146Cholesterol (high)456-2-316-5High LDL3-3-4-3-1-2-4-6High serve200-171-8-3Depression (yes)-24705-1-13Firk serve200-111214Is lyes0-126112-23Physical activity620-112-2-1Cognitive activity620-112-2-1Moderate1-1-10-11-2-1-1-2High-13-3-211-2-23-2-1-1-2-2-1Furits and vegetable0-12611-2-2-1-2-1-2-2-1-2-2-1 <td< td=""><td>Moderate</td><td>-5</td><td>-6</td><td>2</td><td>-1</td><td>2</td><td>0</td><td>- 4</td><td>-6</td></td<>	Moderate	-5	-6	2	-1	2	0	- 4	-6
Smoking         Non-smoker         0         0         0         0         0         0         0         0         0         0           Current smoker         -3         -2         -1         -2         3         1         1         3           Former smoker         0         4         -3         3         -2         -2         3         8           Hypertension (yes)         0         -1         4         5         1         4         4         6           Cholesterol (high)         4         5         6         -2         -3         1         6         -5           High HDL         3         -3         -4         -3         -1         -2         -4         -6           Depression (yes)         -2         4         7         0         5         -1         -1         3           Fish serve         2         0         0         -1         -1         3         -1           Fruits and vegetable         0         -4         -6         -1         -1         -1         3           Fish serve         2         0         -1         1         2         -2	High	-1	_9	3	- 3	0	9	-1	-13
Non-smoker         0         0         0         0         0         0         0         0         0         0         0           Current smoker         -3         -2         -1         -2         3         1         1         3           Former smoker         0         4         -3         3         -2         -2         3         8           Hypertension (yes)         0         -1         4         5         1         4         4         6           Cholesterol (high)         4         5         6         -2         -3         1         6         -5           High HDL         3         -3         -4         -3         -1         -2         -4         -6           Depression (yes)         -2         4         7         0         5         -1         -1         3           Fish serve         2         0         0         -1         -1         0         1         4           Evel send vegetable         0         -4         10         -2         3         4           Is (yes)         0         -1         2         1         -2         3	Smoking	·	-	5	5	Ū.	2		
Current smoker-3-2-1-23113Former smoker04-33-2-238Hypertension (yes)0-1451446Cholesterol (high)456-2-316-5High HDL3-3-4-3-1-2-4-6High LDL2-51771-8-3Depression (yes)-24705-1-13Fish serve200-1771-8-3Depression (yes)-24705-1-13Fish serve2000-1-133-3Depression (yes)0-1200144Is erve2000-1-133Fish serve2000-1-133-2Is grade (yes)495051-233-2Is lysical activity620-112-2-1-1Low00-1-112-2-1-1Is lysical activity000-1-12-2-1High-13 <td>Non-smoker</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td> <td>0</td>	Non-smoker	0	0	0	0	0	0	0	0
Former smoker04-33-2-238Hypertension (yes)0-11451446Cholesterol (high)456-2-316-5High HDL3-3-4-3-11-2-4-6High kDL2-51771-8-3Depression (yes)-24705-1-113Fish serve2000-1-101Fruits and vegetable0-4-6-411214Bi (yes)0-1120444Fish serve200-1-101Fruits and vegetable0-4-6-411214Ib (yes)0-120433333Physical activity620-112-2-1-1Low00-1-10-1-2-2-1-1Ibi (high)-13-8-779000Moderate1-1-1-1-1-1-1High-13-8-779000Sleep problem0-55-2103	Current smoker	-3	-2	-1	-2	3	1	1	3
Hypertension (yes)         0         -1         4         5         1         4         4         6           Cholesterol (high)         4         5         6         -2         -3         1         6         -5           High HDL         3         -3         -4         -3         -1         -2         -4         -6           High LDL         2         -5         1         7         7         1         -8         -3           Depression (yes)         -2         4         7         0         5         -1         -1         3           Fish serve         2         0         0         -4         -4         11         2         1         4           Fruits and vegetable         0         -1         2         1         4           Is erve         0         -1         2         1         4           Is erves         0         -1         2         1         4           Is erves         0         -1         2         1         4           Is erves         0         -1         2         1         -2         3           Physical activity <th0< td=""><td>Former smoker</td><td>0</td><td>4</td><td>-3</td><td>3</td><td>-2</td><td>-2</td><td>3</td><td>8</td></th0<>	Former smoker	0	4	-3	3	-2	-2	3	8
Cholesterol (high)456-2-316-5High HDL3-3-4-3-1-2-4-6High LDL2-51771-8-3Depression (yes)-24705-1-13Fish serve2000-1-101Fruits and vegetable0-4-6-411214Bl (yes)0-1261-604Loneliness (yes)495051-23Physical activity620-112-2-1Cognitive activity620-112-2-1Idw00-1112-23Physical activity620-112-23Cognitive activity000-112-2-1Low00-112-2-1-1Idw-13-3-3-7Not includedNot includedIdw-13-25-21-23-2Idw0-55-77900-2Sileep problem0133-2314<	Hypertension (yes)	0	-1	4	5	1	4	4	6
High HDL       3       -3       -4       -3       -1       -2       -4       -6         High HDL       2       -5       1       7       7       1       -8       -3         Depression (yes)       -2       4       7       0       5       -1       -1       3         Depression (yes)       -2       4       7       0       5       -1       -1       3         Fish serve       2       0       0       -1       -1       0       1         Fruits and vegetable       0       -4       -6       -4       11       2       1       4         Bl (yes)       0       -1       2       6       1       -6       4         Loneliness (yes)       4       9       5       0       5       1       -2       3         Physical activity       6       2       0       -1       1       2       -2       -1         Low       0       0       -1       Not included       Not included       Not included       Not included         High       -13       -3       -3       -1       -13       -3       -2       -2	Cholesterol (high)	4	5	6	-2	-3	1	6	-5
High LDL Depression (yes) $-2$ $4$ $7$ $7$ $1$ $-8$ $-3$ Depression (yes) $-2$ $4$ $7$ $0$ $5$ $-1$ $-1$ $3$ Fish serve $2$ $0$ $0$ $0$ $-1$ $-1$ $0$ $1$ Fruits and vegetable $0$ $-4$ $-6$ $-4$ $11$ $2$ $1$ $4$ TBI (yes) $0$ $-1$ $2$ $6$ $1$ $-6$ $0$ $4$ Loneliness (yes) $4$ $9$ $5$ $0$ $5$ $1$ $-2$ $3$ Physical activity $6$ $2$ $0$ $-1$ $1$ $2$ $-2$ $-1$ Cognitive activity $6$ $2$ $0$ $-1$ $1$ $2$ $-2$ $-1$ Low $0$ $0$ $-1$ $-1$ $2$ $-2$ $-1$ $-2$ $3$ Moderate $1$ $-1$ $-1$ $-1$ $-1$ $-1$ $-2$ $-1$ $-1$ High - $-13$ $-3$ $-1$ <	High HDL	3	-3	-4	-3	-1	-2	-4	-6
Depression (yes)         -2         4         7         0         5         -1         -1         3           Fish serve         2         0         0         0         -1         -1         0         1           Fruits and vegetable         0         -4         -6         -4         11         2         1         4           TBI (yes)         0         -1         2         6         1         -6         0         4           Loneliness (yes)         4         9         5         0         5         1         -2         3           Physical activity         6         2         0         -1         1         2         -2         -1           Cognitive activity         6         2         0         -1         1         2         -2         -1           Low         0         0         -1         Not included         Not included         Not included         Not included         Not included         -2         -2         -1           Low         0         0         -1         -1         -1         -1         -1         -1         -1         -1         -1         -1         -1	High LDL	2	-5	1	7	7	1	-8	-3
Fish serve       2       0       0       0       -1       -1       0       1         Fruits and vegetable       0       -4       -6       -4       11       2       1       4         TBl (yes)       0       -1       2       6       1       -6       0       4         Loneliness (yes)       4       9       5       0       5       1       -2       3         Physical activity       6       2       0       -1       1       2       -2       -1         Cognitive activity       6       2       0       -1       1       2       -2       -1         Low       0       0       -1       Not included       Not included       Not included       Not included         Low       0       0       -1       -1       2       -2       -1         High       -13       -8       -1       -1       Not included       Not included       Not included         Kirai fibrillation       3       2       5       -2       10       3       3       -2         Hearing loss       4       0       0       2       -2       3       1<	Depression (ves)	-2	4	7	0	5	-1	-1	3
Fruits and vegetable0 $-4$ $-6$ $-4$ $11$ $2$ $1$ $4$ TBl (yes)0 $-1$ $2$ $6$ $1$ $-6$ $0$ $4$ Loneliness (yes) $4$ $9$ $5$ $0$ $5$ $1$ $-2$ $3$ Physical activity $6$ $2$ $0$ $-1$ $1$ $2$ $-2$ $-1$ Cognitive activity $6$ $2$ $0$ $-1$ $1$ $2$ $-2$ $-1$ Low $0$ $0$ $0$ $-1$ $Not included$ $Not included$ $Not included$ Low $0$ $0$ $0$ $-1$ $-1$ $Not included$ $Not included$ High $-13$ $-1$ $-1$ $-1$ $-1$ $Not included$ $Not included$ Atrial fibrillation $3$ $2$ $5$ $7$ $7$ $9$ $0$ $0$ Sleep problem $0$ $-5$ $5$ $-2$ $10$ $3$ $3$ $-2$ Hearing loss $4$ $0$ $0$ $2$ $-2$ $3$ $1$ $4$ Diabetes $0$ $1$ $3$ $3$ $5$ $6$ $Not included$ MI $-4$ $-2$ $3$ $4$ $Not included$ $1$ $Not included$ $Not included$	Fish serve	2	0	0	0	-1	-1	0	1
TBl (yes)       0       -1       2       6       1       -6       0       4         Loneliness (yes)       4       9       5       0       5       1       -2       3         Physical activity       6       2       0       -1       1       2       -2       -1         Cognitive activity       6       2       0       -1       1       2       -2       -1         Cognitive activity       6       0       0       -1       1       2       -2       -1         Low       0       0       -1       Not included       Not included       Not included       Not included         Low       0       0       -1       -1       -1       Not included       Not included       Not included         Low       0       0       -1       -1       -1       Not included       Not included       Not included         Low       0       0       -1       -1       -1       Not included       Not included       Not included         Low       0       0       -2       10       3       3       -2       1       4         Itigh       -1       2 <td>Fruits and vegetable</td> <td>0</td> <td>-4</td> <td>-6</td> <td>-4</td> <td>11</td> <td>2</td> <td>1</td> <td>4</td>	Fruits and vegetable	0	-4	-6	-4	11	2	1	4
Loneliness (yes)       4       9       5       0       5       1       -2       3         Physical activity       6       2       0       -1       1       2       -2       -1         Cognitive activity       6       2       0       -1       1       2       -2       -1         Cognitive activity       0       0       -1       Not included       Not included       Not included         Low       0       0       -1       Not included       Not included       Not included       Not included         Low       0       0       -1       -1       1       -2       -2       -1         Moderate       1       -1       -1       Not included       Not included       Not included       Not included         High       -13       -8       -1       -1       -2       10       3       3       -2         Sleep problem       0       -5       5       -2       10       3       3       -2         Hearing loss       4       0       0       2       -2       3       1       4         Diabetes       13       8       Not included       3	TBI (ves)	0	- 1	2	6	1	-6	0	4
Physical activity         6         2         0         -1         1         2         -2         -1           Cognitive activity         Image: Second	Loneliness (ves)	4	9	5	0	5	1	-2	3
Cognitive activityNot includedNot includedNot includedNot includedLow00 $-1$ <	Physical activity	6	2	0	-1	1	2	-2	-1
Low       0       0         Moderate       1       -1         High       -13       -8         Atrial fibrillation       3       2       5       7       7       9       0       0         Sleep problem       0       -5       5       -2       10       3       3       -2         Hearing loss       4       0       0       2       -2       3       1       4         Diabetes       0       1       3       3       5       6       Not included         Kinek       13       8       Not included       3       7       Not included       Not included	Cognitive activity			Not included		Not included		Not included	
Moderate       1       -1         High       -13       -8         Atrial fibrillation       3       2       5       7       7       9       0       0         Sleep problem       0       -5       5       -2       10       3       3       -2         Hearing loss       4       0       0       2       -2       3       1       4         Diabetes       0       1       3       3       5       6       Not included         Kroke       13       8       Not included       3       7       Not included       Not included	Low	0	0						
High $-13$ $-8$ Atrial fibrillation32577900Sleep problem0 $-5$ 5 $-2$ 1033 $-2$ Hearing loss4002 $-2$ 314Diabetes013356Not includedStroke138Not included37Not includedMI $-4$ $-2$ 34Not includedNot included	Moderate	1	-1						
Atrial fibrillation       3       2       5       7       7       9       0       0         Sleep problem       0       -5       5       -2       10       3       3       -2         Hearing loss       4       0       0       2       -2       3       1       4         Diabetes       0       1       3       3       5       6       Not included         Stroke       13       8       Not included       3       7       Not included       Not included	High	-13	-8						
Sleep problem       0       -5       5       -2       10       3       3       -2         Hearing loss       4       0       0       2       -2       3       1       4         Diabetes       0       1       3       3       5       6       Not included         Stroke       13       8       Not included       3       7       Not included         MI       -4       -2       3       4       Not included       Not included	Atrial fibrillation	3	2	5	7	7	9	0	0
Hearing loss4002-2314Diabetes013356Not includedStroke138Not included37Not includedMI-4-234Not includedNot included	Sleep problem	0	-5	5	-2	10	3	3	-2
Diabetes013356Not includedStroke138Not included37Not includedMI-4-234Not includedNot included	Hearing loss	4	0	0	2	-2	3	1	4
Stroke138Not included37Not includedMI-4-234Not includedNot included	Diabetes	0	1	3	3	5	6	Not included	
MI $-4$ $-2$ $3$ $4$ Not included Not included	Stroke	13	8	Not included		3	7	Not included	
	MI	-4	-2	3	4	Not included		Not included	

Table 3 Points for DemNCD risk tools associated with dementia, stroke, MI, and diabetes following Fine and Gray sub distribution hazards model

		Deme	entia		Strok	e		МІ			Diabe	etes	
Validation data		n	Harrel' C	95% CI	n	Harrel'C	95% CI	n	Harrel' C	95% CI	n	Harrel' C	95% CI
Combined data	Male	4862	0.68	(0.65, 0.70)	5073	0.58	(0.54,0.61)	4631	0.65	(0.61, 0.68)	4607	0.68	(0.64,0.72)
	Female	6924	0.65	(0.63, 0.67)	7323	0.55	(0.52, 0.57)	7205	0.65	(0.62, 0.68)	6807	0.61	(0.57, 0.65)
Data component	ts												
ARIC	Male	801	0.72	(0.68, 0.76)	761	0.63	(0.55, 0.70)	665	0.59	(0.52, 0.67)	536	0.61	(0.54, 0.68
	Female	1104	0.74	(0.71, 0.78)	1043	0.60	(0.54, 0.66)	990	0.68	(0.62, 0.73)	771	0.59	(0.51, 0.67)
CFAS I	Male	1707	0.67	(0.62, 0.72)	1606	0.56	(0.49, 0.63)	1495	0.49	(0.39, 0.59)	1645	0.64	(0.56, 0.72)
	Female	2550	0.68	(0.64, 0.71)	2473	0.60	(0.53, 0.67)	2447	0.63	(0.52, 0.74)	2489	0.55	(0.47, 0.64)
CFAS II	Male	1048	0.64	(0.53, 0.75)	971	0.50	(0.34, 0.67)	887	0.53	(0.12, 0.95)	885	0.65	(0.54, 0.76)
	Female	1175	0.75	(0.68, 0.82)	1129	0.75	(0.61, 0.89)	1156	0.59	(0.45, 0.74)	1077	0.53	(0.40, 0.66)
CHS	Male	476	0.67	(0.60, 0.74)	828	0.58	(0.53, 0.63)	739	0.53	(0.49, 0.58)	669	0.65	(0.57, 0.72)
	Female	704	0.70	(0.65, 0.75)	1156	0.58	(0.54, 0.61)	1106	0.56	(0.52, 0.61)	989	0.67	(0.60, 0.73)
FHS	Male	190	0.60	(0.52, 0.68)	374	0.50	(0.41, 0.59)	269	0.54	(0.44 0.64)	318	0.56	(0.40, 0.72)
	Female	290	0.43	(0.37, 0.48)	540	0.63	(0.57, 0.68)	435	0.48	(0.39, 0.58)	478	0.57	(0.43, 0.71)
ADAMS	Male	77	0.65	(0.52, 0.79)	74	0.75	(0.45, 1.00)	NA			65	0·42	(0.00, 0.87)
	Female	81	0.70	(0.59, 0.82)	78	0.59	(0.26, 0.92)				83	0.66	(0.33, 0.99)
MAAS	Male	81	0.60	(0.31, 0.89)	NA			73	0.45	(0.16, 0.73)	76	0.54	(0.26, 0.82)
	Female	79	0.45	(0.32, 0.57)	N/A			77	0.77	(0.98, 0.96)	67	0.77	(0.64, 0.90)
MAP	Male	170	0.69	(0.60, 0.78)	170	0.79	(0.64, 0.94)	155	0.64	(0.47, 0.81)	150	0.73	(0.61, 0.86)
	Female	506	0.74	(0.69, 0.79)	480	0.58	(0.47, 0.69)	487	0.58	(0.44, 0.72)	476	0.64	(0.55, 0.73)
MAS	Male	150	0.70	(0.62, 0.79)	142	0.59	(0.41, 0.78)	127	0.47	(0.23, 0.72)	128	0.39	(0.26, 0.53)
	Female	184	0.63	(0.55, 0.72)	179	0.53	(0.36, 0.69)	169	0.49	(0.24, 0.74)	165	0.76	(0.65, 0.87)
SLAS I	Male	162	0.72	(0.59, 0.85)	147	0.65	(0.40, 0.91)	151	0.49	(0.30, 0.68)	135	0.66	(0.54, 0.78)
	Female	251	0.74	(0.57, 0.91)	245	0.59	(0.30, 0.87)	249	0.46	(0.29, 0.63)	212	0.48	(0.24, 0.72)

Table 4 Predictive accuracy of the DemNCD tool following Fine and Gray model [Harrel'C (95% CI)] associated with the diagnosis of dementia, stroke, MI, and diabetes

However, there are key differences in underlying population characteristics where the above risk tools were employed. The TMTI was developed and validated among patients who were using aspirin, and the Essen risk score was based on a population with cardiovascular risk. The INHEART risk score is the only risk score validated using data with non-laboratory-based risk factors similar to ours [17]. Note that while cardiovascular risk tools generally yield c-statistics closer to 0.7–0.8 [14, 61] when applied to samples of adults of all ages, analyses specifically focused on older adults typically result in c-statistics ranging from 0.58 to 0.65 [58, 60, 62, 63]. A recent report found that the relative risk associated with various cardiovascular risk factors including obesity, hypertension, diabetes, dyslipidaemia, smoking, and physical inactivity decreases with increasing age, providing lower C-statistics for MI and stroke among older adults compared with all age groups [58, 60] including early life, midlife, and latelife. In general, while the literature has documented the weak performance of various risk assessment tools among older adults, these findings have not been widely recognized.

For diabetes, we observed somewhat lower C-statistics/ AUC (95% CI) estimates compared to existing diabetes risk scores [18] where AUC for the risk models involving self-reported variables generally ranged between 0.7 and 0.8. This might be due to our use of late-life cohorts in developing and validating diabetes risk. Most prior diabetes risk tools were developed using mid-life to early late-life cohorts [18].

We observed a paradoxical association between risk factors including obesity, alcohol consumption, high HDL and hypertension with dementia, diabetes, and stroke especially for older women. Similar results are also reported eslewhere [64–68] for older adults. Older adults undergo substantial physical changes leading twowards disability and frailty. Thus, the relationship between these risk factors assessed in midlife may not be relevant to later life risk.

Although we aimed to show that our proposed Dem-NCD risk tools are comparable with the existing risk tools, we acknowledge that the proper comparison of the various risk tools would need to be conducted within a single dataset using same methodology, which is beyond the scope of present paper. While model

Table 5	Comparison of sensitivit	y and specificity for a (	given cut-off of DemNCD risk scores for p	oredicting dementia

Outcomes (DemNCD score	Percentile	Cut-off	Model data		Validation data			
range)	cutoff (≥)	Score	sHR (95% CI)	Sensitivity (%)	Specificity (%)	sHR	Sensitivity (%)	Specificity (%)
For males								
Dementia (model data: –33,	16.6%	-6	2.16 (1.45, 3.21)	96.3	18.7	1.31 (0.82, 2.07)	94.0	18.1
72; validation data: -34, 44)	33.3%	1	3.05 (2.08, 4.46)	87.7	37.5	1.67 (1.09, 2.61)	85.8	36.6
	50%	8	4.59 (3.18, 6.63)	75.6	55.1	2.97 (1.96, 4.48)	74.0	55.0
	66.7%	14	5.89 (4.11, 8.46)	58.3	70.9	3.45 (2.32, 5.15)	57.7	69.5
	83.3%	21	10.43 (7.34, 14.81)	36.1	86.2	5.74 (3.89, 8.47)	33.5	86.1
Stroke (model data: –18, 32;	16.6%	- 1	0.99 (0.71, 1.37)	86.0	21.8	1.12 (0.68, 1.84)	88.7	21.7
validation: – 16, 29)	33.3%	1	1.09 (0.83, 1.44)	77.0	35.0	1.74 (1.18, 2.57)	80.3	34.0
	50%	4	1.46 (1.09, 1.94)	60.0	56.7	1.59 (1.03, 2.47)	57.3	55.5
	66.7%	6	2.06 (1.60, 1.52)	46.6	69.6	1.57 (104, 2.37)	44.7	67.8
	83.3%	10	2.16 (1.66, 2.82)	21.1	87.0	2.59 (1.76, 3.81)	26.3	85.4
Myocardial infarction (model	16.6%	4	1.83 (1.27, 2.64)	93.3	20.3	1.84 (1.16, 2.90)	92.7	20.8
data: –7, 45; validation: –6,	33.3%	7	3.39 (2.45, 4.67)	84.0	35.2	3.19 (2.14, 4.77)	82·4	35.1
47)	50%	12	3.42 (2.46, 4.76)	64·2	53.5	3.18 (2.11, 4.79)	62·0	53.1
	66.7%	16	3.89 (2.77, 5.48)	46.9	71.1	2.28 (1.43, 3.63)	42.9	70.9
	83.3%	20	5.50 (3.99, 7.57)	33.2	85.0	4.91 (3.38, 7.36)	31.3	84.9
Diabetes (model data: -18, 37;	16.6%	-2	1.84 (1.20, 2.83)	91.9	18.4	1.01 (0.55, 1.84)	90.8	18.6
validation: -20, 35)	33.3%	3	1.52 (0.89, 2.60)	75.9	41.8	1.73 (0.90, 3.33)	79.7	42.0
	50%	5	1.85 (1.19, 2.88)	70.7	52.5	1.65 (0.94, 2.91)	72.8	52·3
	66.7%	8	3.41 (2.23, 5.21)	57.9	71.4	2.80 (1.62, 4.82)	59.0	71.7
	83·3%	13	6.33 (4.28, 9.36)	40.4	84.9	5.65 (3.45, 9.25)	42·2	85.2
For females								
Dementia (model data: –36,	16.6%	-11	1.44 (1.13, 1.85)	94.9	19.5	1.63 (1.16, 2.30)	95.0	19.0
47; validation: – 34, 44)	33.3%	-4	1.80 (1.41, 2.29)	85.6	38.6	2.13 (1.53, 2.98)	84.5	38.4
	50%	2	2.46 (1.95, 3.09)	75.0	55.4	2.58 (1.87, 3.56)	72.7	54.3
	66.7%	9	3.56 (2.86, 4.44)	59.2	71.1	3.71 (2.72, 5.07)	55.7	70.6
	83.3%	19	5.05 (4.05, 6.29)	33.7	87.7	4.60 (3.37, 6.29)	29.7	86.7
Stroke (model data: –24, 27;	16.6%	-1	1.03 (0.83, 1.28)	82·3	21.5	0.74 (0.54, 1.02)	80.7	22.3
validation: –22, 29)	33.3%	1	0.99 (0.81, 1.20)	70.5	34.4	0.86 (0.66, 1.12)	72·1	34.2
	50%	4	0.87 (0.71, 1.10)	52.8	54.6	0.77 (0.57, 1.03)	53.5	54.8
	66.7%	6	1.00 (0.82, 1.23)	40.3	69.6	0.83 (0.63, 1.10)	41.8	68.9
	83·3%	9	1.56 (1.30, 1.88)	24.2	85.8	1.41 (1.11, 1.81)	26.8	85.0
Myocardial infarction (model	16.6%	6	1.12 (0.84, 1.50)	90.2	19.8	0.97 (0.67, 1.40)	88.3	19.1
data: –7, 43; validation: –7,	33.3%	9	1.28 (0.93, 1.76)	78.8	39.5	1.25 (0.85, 1.85)	75.7	39.3
44)	50%	11	1.67 (1.27, 2.20)	71.1	52·1	1.12 (0.77, 1.64)	65.7	52.4
	66.7%	14	2.27 (1.75, 2.94)	56.2	69.7	1.72 (1.22, 2.43)	54.8	69.2
	83.3%	19	4.77 (3.73, 6.10)	36.1	87.5	3.14 (2.27, 4.33)	34.3	86.4
Diabetes (model data: -42, 45;	16.6%	-5	1.38 (0.95, 2.00)	91.1	18.1	0.82 (0.50, 1.35)	87.5	17.6
validation: -40, 45)	33.3%	1	1.90 (1.31, 2.74)	80.1	36.6	1.86 (1.20, 2.90)	78.1	36.6
	50%	5	1.79 (1.25, 2.57)	68.1	51.2	1.11 (0.69, 1.77)	62.6	50.7
	66.7%	9	2.62 (1.87 3.66)	55.1	68·2	1.37 (0.88, 2.14)	51.4	67.7
	83.3%	15	6.05 (4.41, 8.29)	34.7	86.3	3.68 (2.47, 5.47)	31.6	86.1

sHR, sub distribution hazards

selection can narrow the set of risk factors and may improve prediction, such analysis is beyond the scope of this paper because of heterogeneity of our cohorts. Such an approach can be tested in future research. Our study had strengths and limitations. The large number of cohorts with standardized measures provides a large set of covariates, which may not be possible with a single cohort where some covariates are entirely missing.



Fig. 1 AUC of the DemNCD-LR tool following logistic regression associated with the diagnosis of dementia, MI, stroke, and diabetes

Multi-country cohort data in the development and validation of the risk tools enhances the generalisability of the DemNCD risk tool to a wide range of populations. However, the cohorts were heterogeneous in terms of sample size, length of follow-up and age of recruitment, and outcome measures. We opted to conduct meta-analyses of regression coefficients from individual cohorts to avoid the effect of cohorts with large sample sizes on the final estimated regression coefficients. We were unable to estimate the baseline risk of the outcomes or provide the 5or 10-year risk score for each of the individual outcomes because of because we used meta analysis of regression coefficients from individual cohorts. Moreover, different diagnostic methods for dementia, stroke, MI, and diabetes across cohorts may cause potential biases. To assess the impact of this and other cohort specific biases, we studied the cohort-specific prediction in addition to aggregate predictions for all cohorts. Yet, the use of heterogeneous datasets for calculating risk scores is increasing in the literature (e.g., PREVENT [69], the American Heart Association's new cardiovascular disease risk tool) due to the benefit of having large contemporary sample that may produce more accurate risk score for diverse groups of the population.

The performance of DemNCD risk tool is very similar to an age only model. This is because all modifiable dementia risk factors increases with age and accumulate over time. Older age often serves as an indicator of time and risk exposure, functioning as a proxy measure for underlying cumulative exposure of life time risk factors. As a result, age is the most significant predictor of dementia, the performance of an age only model in dementia risk assessment is very similar to various risk models that included age and other risk factors [9, 70]. However, age itself is merely a measure of time and lacks biological or causal attributes. So, it does not fundamentally explain risk or its modification. The recent Lancet commission suggests that 14 dementia risk factors account for 45.3% of the population attributable risk of dementia [4]. Early identification of high-risk individuals could improve risk perceptions and help health professionals to recommend interventions that mitigate such risks.

In this paper, we considered a large number of risk/ protective factors across all four conditions irrespective of their statistical significance in our data analysis. This may potentially cause low C-statistics. However, all of these risk/protective factors were considered based on the literature and expert panel judgment, existing risk tools, and current recommendations. Therefore, consideration of all of these risk/protective factors in community settings and in intervention studies may provide great scope in risk identification and behavioral changes to enhance risk reduction for dementia and other NCDs.

### Conclusions

The novel DemNCD-Risk tool provides risk information for dementia and three other cadiometabolic conditions (stroke, MI, and diabetes), on the basis of a single assessment. It has been shown to provide efficient and reasonable predictive properties for all of these outcomes. The tool has the potential to be used in community and clinical settings, primary care and for policy development in preventive health.

### Abbreviations

Myocardial infarction
Logistic regression
Area under the curve
Confidence Interval
Non-communicable disease
Dementia and other NCD
Atherosclerosis Risk in Communities
Cardiovascular Health Study
Framingham Heart Study
Cognitive function and Ageing Studies
Sydney Memory and Aging Study
Maastricht Aging Study
Health and Retirement Study-Aging, Demographics, and
Memory Study
RUSH Memory and Aging project
Singapore Longitudinal Ageing Study-I
World Health Organization
Body mass index
Atrial fibrillation
Traumatic brain injury
Sub-distribution hazards

### **Supplementary Information**

The online version contains supplementary material available at https://doi. org/10.1186/s12916-024-03711-6.

Additional file 1: Section S1 a brief description of the study datasets. Table S1 definition of outcome. Fig. S1. Flowchart showing the process of selecting predictors for the four outcomes, Table S2 distribution of covariates and outcome in each of the dataset under investigation. Table S3 definition of covariates used in the process of harmonization of covariates from different cohort dataset. Table S4 Regression coefficients (95% CI) obtained through meta-analysis following logistic regression model. Table S5 points for DemNCD-LR risk prediction tool. Table S6 validation results of DemNCD-LR risk prediction tool. Table S7 Hosmer Lemeshow goodness of fit for the DemNCD-LR in the validation dataset. Fig. S2. Calibration plot of observed against expected probabilities for assessment of DemNCD-LR performance for predicting dementia. Fig. S3. Calibration plot of observed against expected probabilities for assessment of DemNCD-LR performance for predicting stroke. Fig. S4. Calibration plot of observed against expected probabilities for assessment of DemNCD-LR performance for predicting MI. Fig. S5. Calibration plot of observed against expected probabilities for assessment of DemNCD-LR performance for predicting diabetes. Table S8 Comparison of sensitivity, specificity for a given cutoff of DemNCD-LR risk scores for males and females. Table S9 validation of DemNCD and DemNCD-LR risk tools with age only model in the combined sample.

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### Authors' contributions

KJA is the lead investigator of this study and oversaw the project development, co-developed the original project idea; contributed towards developing the analysis plan, study design including identifying various cohort studies, applied to various studies and got approval, and planned the harmonisation of outcomes and predictors. HH contributed towards study design including identifying various cohort studies, planning the harmonisation of outcomes and predictors, conducted the analysis and drafted the paper. RP co-developed the original project idea; contributed towards developing the analysis plan, study design including identifying various cohort studies and planned the harmonisation of outcomes and predictors. SK contributed towards study design including identifying various cohort studies, applied to various studies, got approval, and planned the harmonisation of outcomes and predictors. KK contributed towards developing the analysis plan, study design including identifying various cohort studies, and planning the harmonisation of outcomes and predictors. CSA, MB, HB, PSS, MC, ALF, RW, MK, LJ, SK, NL, OL, FM, JES, provided inputs to the analysis. All authors critically reviewed and contributed to the manuscript and approved the final draft.

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### Data availability

No datasets were generated or analysed during the current study.

### Declarations

### Ethics approval and consent to participants

Ethics approval is provided by the University of New South Wales Human Research Ethics Committee (UNSW HREC; protocol numbers HC200515, HC3413). All data are de-identified and stored on a secure server at Neuroscience Research Australia. All the participants consented to the original data collection and individual studies each received ethical/IRB approval.

### **Consent for publication**

Not applicable.

### **Competing interests**

JES has received honoraria for scientific advisory, lectures, and clinical research from Pfizer; Roche; Zuellig Pharma; Astra Zeneca; Sanofi; Novo Nordisk; MSD; Eli Lilly; Abbott; Mylan; Boehringer Ingelheim. CSA has received grants from Takeda.

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### References

- Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–46.
- World Health Organization. Risk reduction of cognitive decline and dementia: WHO guidelines. 2019.
- Tai XY, Veldsman M, Lyall DM, Littlejohns TJ, Langa KM, Husain M, et al. Cardiometabolic multimorbidity, genetic risk, and dementia: a prospective cohort study. Lancet Healthy Longev. 2022;3(6):e428–36.
- Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, et al. Dementia prevention, intervention, and care: 2024 report of the lancet standing Commission. Lancet. 2024;404:572.
- Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64(2):277–81.
- Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA Neurol. 2017;74(10):1246–54.
- Anstey KJ, Ee N, Eramudugolla R, Jagger C, Peters R. A systematic review of meta-analyses that evaluate risk factors for dementia to evaluate the quantity, quality, and global representativeness of evidence. J Alzheimer's Dis. 2019;70(s1):S165–86.
- Anstey KJ, Peters R, Mortby ME, Kiely KM, Eramudugolla R, Cherbuin N, et al. Association of sex differences in dementia risk factors with sex differences in memory decline in a population-based cohort spanning 20–76 years. Sci Rep. 2021;11(1):7710.
- Huque MH, Kootar S, Eramudugolla R, Han SD, Carlson MC, Lopez OL, et al. CogDrisk, ANU-ADRI, CAIDE, and LIBRA risk scores for estimating dementia risk. JAMA Network Open. 2023;6:e2331460.
- Anstey KJ, Zheng L, Peters R, Kootar S, Barbera M, Stephen R, et al. Dementia risk scores and their role in the implementation of risk reduction guidelines. Front Neurol. 2022;12:2436.
- Anstey KJ, Kootar S, Huque MH, Eramudugolla R, Peters R. Development of the CogDrisk tool to assess risk factors for dementia. Alzheimer's Dementia: Diagn Assess Dis Monit. 2022;14(1): e12336.
- D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. Framingham Study Stroke. 1994;25(1):40–3.
- Parmar P, Krishnamurthi R, Ikram MA, Hofman A, Mirza SS, Varakin Y, et al. The Stroke Riskometer<sup>™</sup> app: validation of a data collection tool and stroke risk predictor. Int J Stroke. 2015;10(2):231–44.

- Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. bmj. 2017;357:j2099.
- Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835–42.
- Boulanger M, Li L, Lyons S, Lovett NG, Kubiak MM, Silver L, et al. Essen risk score in prediction of myocardial infarction after transient ischemic attack or ischemic stroke without prior coronary artery disease. Stroke. 2019;50(12):3393–9.
- McGorrian C, Yusuf S, Islam S, Jung H, Rangarajan S, Avezum A, et al. Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART Modifiable Risk Score. Eur Heart J. 2011;32(5):581–9.
- Noble D, Mathur R, Dent T, Meads C, Greenhalgh T. Risk models and scores for type 2 diabetes: systematic review. Bmj. 2011;343.
- Farnsworth von Cederwald B, Josefsson M, Wåhlin A, Nyberg L, Karalija N. Association of cardiovascular risk trajectory with cognitive decline and incident dementia. Neurology. 2022;98(20):e2013–22.
- Jia R, Wang Q, Huang H, Yang Y, Chung YF, Liang T. Cardiovascular disease risk models and dementia or cognitive decline: a systematic review. Front Aging Neuroscience. 2023;15:1257367.
- Iturria-Medina Y, Sotero RC, Toussaint PJ, Mateos-Pérez JM, Evans AC. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. Nat Commun. 2016;7(1): 11934.
- 22. Low L, Anstey K. Dementia literacy: recognition and beliefs on dementia of the Australian public. Alzheimer's Dementia. 2009;5(1):43–9.
- Heger I, Deckers K, van Boxtel M, de Vugt M, Hajema K, Verhey F, et al. Dementia awareness and risk perception in middle-aged and older individuals: baseline results of the MijnBreincoach survey on the association between lifestyle and brain health. BMC Public Health. 2019;19(1):1–9.
- 24. World Health Organization. Global action plan on the public health response to dementia 2017–2025. 2017.
- Chong TW, Rego T, Lai R, Westphal A, Pond CD, Curran E, et al. Preferences and perspectives of Australian general practitioners towards a new "fourin-one" risk assessment tool for preventative health: the LEAD! GP Project J Alzheimer's Dis. 2023;94(2):801–14.
- Kootar S, Huque MH, Kiely KM, Anderson CS, Jorm L, Kivipelto M, et al. Study protocol for development and validation of a single tool to assess risks of stroke, diabetes mellitus, myocardial infarction and dementia: DemNCD-Risk. BMJ Open. 2023;13(9): e076860.
- 27. Investigators ARIC. The atherosclerosis risk in communit (ARIC) study: design and objectives. Am J Epidemiol. 1989;129(4):687–702.
- Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The cardiovascular health study: design and rationale. Ann Epidemiol. 1991;1(3):263–76.
- 29. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. American Journal of Public Health and the Nations Health. 1951;41(3):279–86.
- Brayne C, McCracken C, Matthews FE. Cohort profile: the Medical Research Council cognitive function and ageing study (CFAS). Int J Epidemiol. 2006;35(5):1140–5.
- Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. The Lancet. 2013;382(9902):1405–12.
- Sachdev PS, Brodaty H, Reppermund S, Kochan NA, Trollor JN, Draper B, et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70–90 years. Int Psychogeriatr. 2010;22(8):1248–64.
- Schievink SH, van Boxtel MP, Deckers K, van Oostenbrugge RJ, Verhey FR, Köhler S. Cognitive changes in prevalent and incident cardiovascular disease: a 12-year follow-up in the Maastricht Aging Study (MAAS). Eur Heart J. 2022;43(7):e2–9.
- Langa KM, Plassman BL, Wallace RB, Herzog AR, Heeringa SG, Ofstedal MB, et al. The aging, demographics, and memory study: study design and methods. Neuroepidemiology. 2005;25(4):181–91.

- Bennett DA, Schneider JA, Buchman AS, Mendes de Leon C, Bienias JL, Wilson RS. The rush memory and aging project: study design and baseline characteristics of the study cohort. Neuroepidemiology. 2005;25(4):163–75.
- Ng TP, Jin A, Feng L, Nyunt MSZ, Chow KY, Feng L, et al. Mortality of older persons living alone: Singapore longitudinal ageing studies. BMC Geriatr. 2015;15:1–9.
- Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PLoS ONE. 2018;13(3): e0194127.
- Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. BMJ Open. 2019;9(1):e022846.
- Yu J-T, Xu W, Tan C-C, Andrieu S, Suckling J, Evangelou E, et al. Evidencebased prevention of Alzheimer's disease: systematic review and metaanalysis of 243 observational prospective studies and 153 randomised controlled trials. J Neurol Neurosurg Psychiatry. 2020;91(11):1201–9.
- 40. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol. 2013;74(4):580–91.
- Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, et al. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. J Am Heart Assoc. 2016;5(9): e002495.
- 42. Huang Y, Cai X, Li Y, Su L, Mai W, Wang S, et al. Prehypertension and the risk of stroke: a meta-analysis. Neurology. 2014;82(13):1153–61.
- Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. Lancet (London, England). 2013;383(9921):970–83.
- Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. The lancet. 2017;390(10113):2673–734.
- 45. Anstey KJ, Cherbuin N, Herath PM. Development of a new method for assessing global risk of Alzheimer's disease for use in population health approaches to prevention. Prev Sci. 2013;14(4):411–21.
- 46. Deckers K, van Boxtel MP, Schiepers OJ, de Vugt M, Muñoz Sánchez JL, Anstey KJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr Psychiatry. 2015;30(3):234–46.
- Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. The Lancet Neurology. 2006;5(9):735–41.
- Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. Circulation. 2009;119(24):3078–84.
- D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743–53.
- Wilson PW, Meigs JB, Sullivan L, Fox CS, Nathan DM, D'Agostino RB. Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. Arch Intern Med. 2007;167(10):1068–74.
- Chen L, Magliano DJ, Balkau B, Colagiuri S, Zimmet PZ, Tonkin AM, et al. AUSDRISK: an Australian Type 2 Diabetes Risk Assessment Tool based on demographic, lifestyle and simple anthropometric measures. Med J Aust. 2010;192(4):197–202.
- von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. Sociological Methods & Research. 2020;49(3):699–718.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.
- Huque MH, Carlin JB, Simpson JA, Lee KJ. A comparison of multiple imputation methods for missing data in longitudinal studies. BMC Med Res Methodol. 2018;18(1):1–16.
- Austin PC, Lee DS, D'Agostino RB, Fine JP. Developing points-based risk-scoring systems in the presence of competing risks. Stat Med. 2016;35(22):4056–72.
- Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA. 1982;247(18):2543–6.

- 57. Hosmer DW Jr. Lemeshow S, Sturdivant RX. Applied logistic regression: John Wiley & Sons; 2013.
- Livingstone S, Morales DR, Donnan PT, Payne K, Thompson AJ, Youn J-H, et al. Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study. The lancet Healthy longevity. 2021;2(6):e352–61.
- van Os HJ, Kanning JP, Ferrari MD, Bonten TN, Kist JM, Vos HMM, et al. Added predictive value of female-specific factors and psychosocial factors for the risk of stroke in women under 50. Neurology. 2023;101(8):e805–14.
- Kaneko H, Yano Y, Okada A, Itoh H, Suzuki Y, Yokota I, et al. Age-dependent association between modifiable risk factors and incident cardiovascular disease. J Am Heart Assoc. 2023;12(2): e027684.
- Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. The Lancet. 2018;391(10133):1897–907.
- 62. Verweij L, Peters RJ, op Reimer WJS, Boekholdt SM, Luben RM, Wareham NJ, et al. Validation of the Systematic COronary Risk Evaluation-Older Persons (SCORE-OP) in the EPIC-Norfolk prospective population study. Int J Cardiol. 2019;293:226–30.
- Mehta S, Jackson R, Poppe K, Kerr AJ, Pylypchuk R, Wells S. How do cardiovascular risk prediction equations developed among 30–74 year olds perform in older age groups? A validation study in 125 000 people aged 75–89 years. J Epidemiol Community Health. 2020;74(6):527–33.
- Mielke MM, Zandi P, Sjogren M, Gustafson D, Ostling S, Steen B, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005;64(10):1689–95.
- Sabia S, Fayosse A, Dumurgier J, Dugravot A, Akbaraly T, Britton A, et al. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. bmj. 2018;362:k2927.
- 66. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth W, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009;66(3):336–42.
- Odden MC, Rawlings AM, Arnold AM, Cushman M, Biggs ML, Psaty BM, et al. Patterns of cardiovascular risk factors in old age and survival and health status at 90. The Journals of Gerontology: Series A. 2020;75(11):2207–14.
- Rodgers JL, Jones J, Bolleddu SI, Vanthenapalli S, Rodgers LE, Shah K, et al. Cardiovascular risks associated with gender and aging. Journal of cardiovascular development and disease. 2019;6(2): 19.
- Khan SS, Coresh J, Pencina MJ, Ndumele CE, Rangaswami J, Chow SL, et al. Novel prediction equations for absolute risk assessment of total cardiovascular disease incorporating cardiovascular-kidney-metabolic health: a scientific statement from the American Heart Association. Circulation. 2023;148(24):1982–2004.
- Kivimäki M, Livingston G, Singh-Manoux A, Mars N, Lindbohm JV, Pentti J, et al. Estimating dementia risk using multifactorial prediction models. JAMA Network Open. 2023;6(6):e2318132-e.

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