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Gender-specific clinical risk scores incorporating blood pressure variability for predicting incident dementia

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Abstract

Introduction: The present study examined the gender-specific prognostic value of blood pressure (BP) and its variability in the prediction of dementia risk and developed a score system for risk stratification.

Method: This was a retrospective, observational population-based cohort study of patients admitted to government-funded family medicine clinics in Hong Kong between January 1st, 2000 to March 31st, 2002 with at least three blood pressure measurements. Gender-specific risk scores for dementia were developed and tested.

Results: The study consisted of 74855 patients, of whom 3550 patients (incidence rate: 4.74%) developed dementia over a median follow-up of 112 months (IQR= [59.8-168]). Nonlinear associations between diastolic/systolic BP measurements and the time to dementia presentation were identified. Gender-specific dichotomized clinical scores were developed for males (age, hypertension, diastolic and systolic BP and their measures of variability) and females (age, prior cardiovascular, respiratory, gastrointestinal diseases, diabetes mellitus, hypertension, stroke, mean corpuscular volume, monocyte, neutrophil, urea, creatinine, diastolic and systolic BP and their measures of variability). They showed high predictive strengths for both male (hazard ratio [HR]: 12.83, 95% confidence interval [CI]: 11.15-14.33, p value<0.0001) and female patients (HR: 26.56, 95% CI: 14.44-32.86, p value<0.0001). The constructed gender-specific scores outperformed the simplified systems without considering BP variability (C-statistic: 0.91 vs. 0.82), demonstrating the importance of BP variability in dementia development.

Conclusion: Gender-specific clinical risk scores incorporating BP variability can accurately predict incident dementia and can be applied clinically for early disease detection and optimized patient management.

Key words: blood pressure variability; risk score; dementia; predictive model

Introduction

Dementia is a global health concern, particularly in the face of the ageing population and its burden upon the healthcare system. Therefore, predictors for dementia are warranted for early diagnosis and intervention to improve patient prognosis. An increase in both systolic and diastolic blood pressure, below the threshold of hypertension, has been reported to be associated with increased dementia risk. [1-3] Moreover, over the past decade, studies have shown that increased blood pressure variability (BPV) was found to be associated with an increased risk of dementia. [4-8] However, its clinical application in dementia risk stratification has yet been explored.

Furthermore, studies have reported apparent gender differences in the risk factors for dementia. [9-11] Several hypotheses have been raised for the increased dementia risk amongst women, including the peri and postmenopausal hormonal changes, difference in apolipoprotein E4 allele inheritance and stronger inflammatory dysregulation. [12-15] In addition, gender affects the clinical presentation of dementia, such as a higher frequency of visual hallucination, depression, sarcopenia and frailty amongst female patients. [16-18] However, there is a lack of research on the identification and application of gender-specific dementia risk factors. Therefore, the present study aims to explore the genetic-specific prognostic value of BP and BPV in the prediction of dementia risk and establish clinical risk scores for risk stratification.

Methods

Research design and data

The present cohort consists of patients admitted to government-funded family medicine clinics between January 1st, 2000 to March 31st, 2002. The patients were identified from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database that centralizes patient information from government-funded hospitals in Hong Kong to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results, and medication prescription details. The system has been previously used by both our team and other teams in Hong Kong [19 20]. Data were obtained regarding consecutive patients diagnosed with dementia, excluding those who died or were discharged within 24 hours after the first diastolic/systolic BP measurement and those with less than three diastolic/systolic BP measurements (study baseline). Mortality data were obtained from the Hong Kong Death Registry, a population-based official government registry with the registered death records of all Hong Kong citizens. Data on the clinical characteristics, disease diagnosis, laboratory results (including complete blood counts, biochemical tests, and diastolic/systolic BP measurements), and medication prescription details were extracted. Dementia were identified with codes from the International Classification of Disease, Nineth Edition (ICD-9): 331.82, 290.0, 290.1, 290.11, 290.12, 290.13, 290.2, 290.21, 290.3, 290.4, 290.41, 290.42, 290.43, 290.8, 290.9, 294.2, 294.1, 294.11, 294.21, 46.1, 42.0, 294.29. The ICD-9 codes for past comorbidities and historical medication prescriptions are detailed in **Supplementary Tables 1 and 2**.

Statistical analysis and primary outcomes

The primary outcome was the development of dementia from the study baseline in a time-to-event analysis. Patients were followed up from their admission date until December 31st 2019. We extracted the baseline/latest/maximum/minimum values of diastolic and systolic BP, and calculated the temporal variability measures of diastolic and systolic BP [21 22]: 1) mean, 2) median, 3) standard deviation (SD), 4) root mean square (RMS) by first squaring all blood pressure values then performing square root of the mean of the squares, 5) coefficient of variation (CV) by dividing the BP SD by the mean BP then multiplying by 100, and 6) a variability score (from 0 [low] to 100 [high]) defined as the number of changes in BP of 5 mmHg or more, i.e., 100*(number of absolute BP change of each two successive measurements>5)/number of measurements.

Clinical characteristics were summarized using descriptive statistics. Continuous variables were presented as median (95% confidence interval [CI] or interquartile range [IQR]) whilst categorical variables were presented as count (%). The Mann- Whitney U test was used to compare continuous variables. The χ^2 test with Yates' correction was used for 2×2 contingency data, and Pearson's χ^2 test was used for contingency data for variables with more than two categories. Univariate Cox regression models were conducted based on male and female subgroups, respectively. Significant univariate predictors of demographics, prior comorbidities, clinical and biochemical tests, medication prescriptions and BP variabilities were used as input of a multivariate Cox analysis model, adjusted by traditional factors and intercepts. Hazard ratios (HRs) with corresponding 95% CI and P values were reported. All statistical tests were two-tailed and considered significant if P value <0.001. Data analyses were performed using RStudio software (Version: 1.1.456) and Python (Version: 3.6).

Results

Gender-specific cohort clinical characteristics

This retrospective cohort study included 74855 patients (male= 39.2%). Over the course of follow-up, 3550 patients (incidence rate: 4.74%, including 1287 males and 2263 females) developed dementia after a median follow-up of 112 months (IQR= [59.8-168], max= 242) after initial BP measurement (**Supplementary Figure 1**). The baseline demographic, biochemical and clinical parameters are summarized in **Table 1** in a gender specific way. The number of patients in male cohort was in less amount in all age intervals except for [0,10], [60,70] and [70,80] years old. Males were more frequently to have past comorbidities of cardiovascular diseases (38.81% v.s. 35.40%, p value<0.0001), respiratory diseases (52.55% v.s. 43.32%, p value<0.0001) and renal complications (25.93% v.s. 16.27%, p value<0.0001), but were less frequently to have diabetes mellitus (13.33% v.s. 14.48%, p value=0.0001), and hypertension (59.05% v.s. 61.15%, p value=0.0043) than females.

In addition, males were more frequently prescribed for angiotensin-converting enzyme inhibitor (ACEI) (17.82% v.s. 13.95%, p value<0.0001), calcium channel blockers (29.57% v.s. 25.60%, p value<0.0001), diuretics for heart failure (5.03% v.s. 4.29%, p value<0.0001), nitrates (11.92% v.s. 10.34%, p value<0.0001), antihypertensive drugs (17.52% v.s. 6.15%, p value<0.0001), and anti-diabetic drugs (11.26% v.s. 10.74%, p value=0.0484)., but were less frequently prescribed angiotensin receptor blocker (ARB) (0.46% v.s. 0.60%, p value=0.0109), diuretics for hypertension (11.94% v.s. 13.58%, p value<0.0001), statins and fibrates (11.99% v.s. 12.56%, p value=0.0427).

Males had lower platelet level (median: 223 x10^9/L, IQR: 184.0-268, max: 1020 x10^9/L v.s. 244 x10^9/L, IQR: 203.0-290.5, max: 1745 x10^9/L, p value<0.0001), high density lipoprotein (HDL) (median: 1.18 mmol/mol, IQR: 1.01-1.39, max: 4.14 v.s. median: 1.37 mmol/mol, IQR: 1.16-1.63, max: 3.29 mmol/mol, p value=0.0104), maximum of diastolic BP (median: 82 mm Hg, IQR: 78-94, max: 150 mm Hg v.s. median: 89 mm Hg, IQR: 75-98, max: 144, p value=0.0145), and baseline value of systolic BP (median: 131 mm Hg, IQR: 123-152, max: 244 v.s. median: 139 mm Hg, IQR: 120-159, max: 251 mm Hg, p value=0.0132). However, male patients had higher urea level (6 mmol/L, IQR: 5.0-7.3, max: 60.9 mmol/L v.s. 5.5 mmol/L, IQR: 4.5-6.8, ， max: 53.4 mmol/L, p value=0.0145), creatinine (median: 99 umol/L, IQR: 88-113, max: 1957 v.s. 77 umol/L, IQR: 68.0-89, max: 1274 umol/L, p value<0.0001), alanine transaminase (median: 22 U/L, IQR: 16.0-33, max: 3909 U/L v.s. 18 U/L, IQR: 13-26, max: 1576 U/L, p value=0.0023),

Endocrine (median age= 73.9, IQR= [63.4-82.2]) and gastrointestinal (median age= 74.5, IQR=[63.6, 82.7]) comorbidities, in addition to diabetes mellitus (median age= 75.6, IQR= [66.4, 83.3]), were the three earliest comorbidities that occurred prior to dementia, with no significant gender differences (**Supplementary Table 3**). The incidence rates of female patients were significantly higher than those of male patients in the following age groups of [40,50], [50-60], [60-70], [70-80], [80-90], and 90+ (**Figure 1**). The breakdown of incidences with respect to gender and age are shown in **Supplementary Table 4** and the baseline characteristics of the dementia subgroup are shown in **Supplementary Table 5**. Kaplan-Meier curves for the freedom from dementia are shown in **Figure 2** whilst those for all-cause mortality are detailed in **Supplementary Figure 2**.

Significant risk predictors of dementia and associations of BP measurements with time-to-dementia

Univariate predictors for incident dementia are summarized in **Table 2**, whilst those for mortality amongst those with dementia are detailed in the **Supplementary Table 6.** With identified significant univariate predictors as inputs, the following parameters were found to be significant multivariate predictors (**Table 3**): 1) age of first BP measurement: 40-50 (HR: 1.05, 95% CI: [1.01, 1.26], p < 0.001), 50-60 (HR: 1.17, 95% CI: [1.06, 1.45], p < 0.001), 60-70 (HR: 1.43, 95% CI: [1.20, 1.93], p: 0.001), 70-80 (HR: 1.45, 95% CI: [1.36, 1.93], p < 0.0001), 80-90 (HR: 1.47, 95% CI: [1.09, 3.06], p < 0.0001); 2) comorbidities: cardiovascular (HR: 1.10, 95% CI: [1.08, 1.55], p < 0.0001), respiratory (HR: 1.56, 95% CI: [1.05, 2.31], p: 0.028), hypertension (HR: 1.21, 95% CI: [1.09, 1.46], p < 0.0001), gastrointestinal (HR: 1.66, 95% CI: [1.23, 2.23], p: 0.001); 3) medication: calcium channel blockers (HR: 1.15, 95% CI: [1.04, 1.57], p < 0.0001), diuretics for hypertension (HR: 1.01, 95% CI: [1.01, 1.44], p < 0.0001); 4) laboratory parameters: eosinophil count (HR: 0.28, 95% CI: [0.10, 0.77], p: 0.014), neutrophil count (HR: 1.03, 95% CI: [1.08, 1.47], p < 0.0001), urate (HR: 0.14, 95% CI: [0.04, 0.53], p: 0.004), aspartate transaminase (HR: 0.99, 95% CI: [0.97, 1.00], p: 0.017); 5) diastolic BP: baseline (HR: 1.02, 95% CI: [1.01, 1.21], p < 0.0001), mean (HR: 1.25, 95% CI: [1.14, 1.57], p < 0.0001), variance (HR: 1.40, 95% CI: [1.04, 1.51], p < 0.0001), CV (HR: 1.31, 95% CI: [1.02, 1.65], p < 0.0001), variability score (HR: 1.22, 95% CI: [1.09, 2.11], p < 0.0001); 6) systolic BP: baseline (HR: 1.02, 95% CI: [1.01, 1.21] p < 0.0001), maximum (HR: 1.40, 95% CI: [1.18, 1.42], p < 0.0001), mean (HR: 1.27, 95% CI: [1.17, 1.61], p < 0.0001), SD (HR: 1.18, 95% CI: [1.01, 1.69], p < 0.0001), variability score (HR: 1.43, 95% CI: [1.18, 1.91], p < 0.0001). Nonlinear relationships between systolic or diastolic BP measurements and the time-to-dementia are shown in **Supplementary Figures 3 and 4**, respectively.

Gender-specific clinical risk score to predict incident dementia

Based on the findings of multivariate Cox regression, cut-off values of significant predictors, excluding predictive post-hoc medication variables, and developed a clincal risk score for early prediction of dementia in male and female patients in **Table 4**. For both genders, the following common variables were used: age, prior hypertension, baseline, median, variance and variability score of diastolic blood pressure and systolic blood pressure. For female patients, the following additional variables were included: prior cardiovascular, respiratory and gastrointestinal diseases, hypertension and stroke, and laboratory examinations.

Furthermore, the details of the score for male and female patients with/without dementia are summarized in **Supplementary Table 7**. Comparing within the gender subgroups, both male (median: 4.22, IQR: 2.36,5.56, max: 9.17 v.s. median: 3.5, IQR: 2.31,4.77, max: 5.47, p value<0.0001), and female (median: 11.58, IQR: 8.82,14.7, max: 26.56 v.s. median: 8.96, IQR: 6.05,12.22, max: 15.81, p value<0.0001) with dementia had a higher score than their non-demented counterparts. The discrimination performance of the scores is shown in **Figure 4**. For females, the score had a cutoff value of 11.13 and is also able to significantly predict the initial presentation of dementia (HR: 1.13, 95% CI: 1.12-1.24, p value<0.0001), and the dichotomized score system shows much more predictive ability (HR: 26.56, 95% CI: 14.44-32.86, p value<0.0001).

The performance of the scores were compared in **Supplementary Table 8** to predict the initial presentation of dementia. For males, the score had a cutoff of 4.48 and can significantly predict initial presentation of dementia (HR: 1.08, 95% CI: 1.05-1.11, p value<0.0001), while the dichotomized score system demonstrated even more predictive strength (HR: 12.83, IQR: 11.15-14.33, p value<0.0001).

To explore further a simpler score that can be used at baseline (rather than incorporating subsequent results which would not be available at that juncture) (**Table 5**). In this simplified score, only baseline blood pressure was included. However, the performance metrics (**Table 6**) showed that there was a reduction in the c-statistic by 0.088 and 0.096 for male and female patients, respectively, indicating the importance of incorporating successive measurements for blood pressure on follow-up to improve risk stratification.

Discussion

The main findings of this study include:

1) A combination of clinical, biochemical and systolic/ diastolic BP value and variability can be used to predict the onset of dementia;
2) There are nonlinear associations between diastolic/systolic BP value and variability and the time to dementia manifestation;
3) A gender-specific, easy-for-use clinical risk score for early prediction of dementia has been constructed and found to be of high predictive strength;
4) The constructed gender-specific clinical risk scores outperformed the simplified scores that excluded BP variability, demonstrating the importance of the latter in dementia development.

The non-linear associations between diastolic and systolic BP value and variability reported by the present study support findings from existing studies. [7 23-25]. There are several hypotheses proposed for the underlying mechanisms of the non-linear relationship observed. Previous studies propose that the apolipoprotein E4 allele upholds a modulatory role in the effects of BP on cognitive function. [26

27] Furthermore, patients with chronic hypertension have been shown to have increased Tau phosphorylation under BP reduction, suggesting that chronic hypertension may increase one's susceptibility to dementia particularly under extreme BP changes. [28 29] Moreover, in a recent study by *Walker et al.*, a pattern of midlife hypertension and late-life hypotension was reported to precede cognitive decline, which suggests a potential early neurological change underlying both the BPV and the cognitive decline. The age-dependent BP change and its associated dementia risk can also be attributed to the non-linear relationship between BP value and the risk of dementia.

Although it remains controversial whether females have a higher risk for dementia, the presence of gender-specific risk factors has been continuously explored. [30 31] First of all, the menopausal transition in middle-aged females was reported to induce a hypometabolic state and can increase brain beta-amyloid deposition thus increase dementia risk, which is supported by the drastic increase in the HR amongst the peri and postmenopausal age groups. [32 33] The loss of cardioprotective effect by estrogen amongst postmenopausal females and resulting BP instability, as reflected by the predictiveness of BPV amongst female patients, may also underly their higher risk for vascular dementia. [34] In addition, it has been reported that a selective survival of males less susceptible to cardiovascular conditions after mid-life can explain the lower dementia risk amongst males, which coincides with the presence of cardiovascular comorbidities as a female-only predictor in the present cohort. [35] Whilst screening assessments such as The Montreal Cognitive Assessment (MoCA) are available for identifying patients with cognitive impairment, carrying out such tests is very time consuming and simple clinical scores that can be used to predict longer term dementia development, not just early cognitive impairment, would be helpful for clinicians to manage the patients accordingly.

The plethora of factors underlying the gender differences in dementia risk demonstrates the importance of a gender-specific risk-stratification score system to increase the chances of early disease detection and optimize patient care.

Limitations

Several limitations should be noted for the present study. Firstly, given its retrospective and observational nature, it is prone to selection bias and susceptible to errors due to under-coding and coding errors. Moreover, due to local data availability, only visit-to-visit BP records could be obtained for the analysis of long term BPV, whereas short-term BPV data were not available. Other important risk factors for dementia, such as the family history of dementia, apolipoprotein E4 allele status, body mass index and smoking status were not routinely coded into structured data. We have indirectly accounted for the influence of cardiovascular risk factors by examining the prognostic value of cardiovascular comorbidities. In addition, the age distribution for male and female dementia patients were different. For example, the age distribution for female dementia patients were wider. This could potentially explain the need for additional BP measurements for the model development. These scores will be validated in the future when additional data become available.

Conclusion

Gender-specific clinical risk scores incorporating BP variability can accurately predict incident dementia and can be applied clinically for early disease detection and optimized patient management.

Data Availability

The dataset for this study can be obtained by contacting the corresponding author(s) upon reasonable request for research purposes.

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Competing Interests Statement

None.

Contributorship Statement

JZ, SL: data analysis, data interpretation, statistical analysis, manuscript drafting, critical revision of manuscript

WTW, KBW, KSKL, TTLL, AKCW, TL, CC: project planning, data acquisition, data interpretation, critical revision of manuscript

BMYC: study supervision, data interpretation, statistical analysis, critical revision of manuscript

QZ, GT: study conception, study supervision, project planning, data interpretation, statistical analysis, manuscript drafting, critical revision of manuscript

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Table 1. Clinical characteristics of male and female patients of the cohort.
* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

	Males (N=29333, event:1287) Median (IQR);Max;N or Count (%)	**Females (N=45522, event: 2263) Median (IQR);Max;N or Count (%)**	**P value**
Demographics			
Age of first BP test, years	64.6(51.5-73.2);99.9;n=29333	62.3(49.0-72.8);101.4;n=45522	0.1201
[0,10]	28(0.09%)	13(0.02%)	0.0003***
[10,20]	287(0.97%)	322(0.70%)	0.0001***
[20,30]	1307(4.45%)	1658(3.64%)	<0.0001***
[30,40]	1303(4.44%)	2644(5.80%)	<0.0001***
[40,50]	3643(12.41%)	7642(16.78%)	<0.0001***
[50,60]	5133(17.49%)	8736(19.19%)	<0.0001***
[60,70]	7395(25.21%)	9804(21.53%)	<0.0001***
[70,80]	7653(26.09%)	10275(22.57%)	<0.0001***
[80,90]	1848(6.30%)	3070(6.74%)	0.026*
90+	338(1.15%)	621(1.36%)	0.0142*
Past comorbidities			
Cardiovascular	11387(38.81%)	16115(35.40%)	<0.0001***
Respiratory	15417(52.55%)	19721(43.32%)	<0.0001***
Renal	7608(25.93%)	7408(16.27%)	<0.0001***
Endocrine	1312(4.47%)	1971(4.32%)	0.382
Diabetes mellitus	3912(13.33%)	6595(14.48%)	0.0001***
Hypertension	17322(59.05%)	27840(61.15%)	0.0043**
Gastrointestinal	11433(38.97%)	17909(39.34%)	0.5139
Stroke	54(0.18%)	85(0.18%)	0.9956
Medications			
ACEI	5229(17.82%)	6353(13.95%)	<0.0001***
ARB	136(0.46%)	277(0.60%)	0.0109*

Calcium channel blockers	8675(29.57%)	11657(25.60%)	<0.0001***
Beta blockers	7457(25.42%)	11316(24.85%)	0.1819
Diuretics for heart failure	1478(5.03%)	1955(4.29%)	<0.0001***
Diuretics for hypertension	3505(11.94%)	6184(13.58%)	<0.0001***
Nitrates	3498(11.92%)	4708(10.34%)	<0.0001***
Antihypertensive drugs	5141(17.52%)	2804(6.15%)	<0.0001***
Anti-Diabetic drugs	3305(11.26%)	4893(10.74%)	0.0484*
Statins and fibrates	3518(11.99%)	5718(12.56%)	0.0427*
Complete blood count tests			
Mean corpuscular volume, fL	90.8(87.5-94.0);132.3;n=11927	89.5(85.9-92.5);133.0;n=18776	0.8711
Basophil, x10^9/L	0.02(0.01-0.03);0.6;n=5397	0.02(0.01-0.02);0.5;n=7871	0.8921
Eosinophil, x10^9/L	0.1(0.1-0.295);9.25;n=6390	0.1(0.1-0.2);8.8;n=9454	0.9324
Lymphocyte, x10^9/L	1.6(1.1-2.15);137.94;n=6462	1.8(1.3-2.3);85.28;n=9572	0.4514
Metamyelocyte, x10^9/L	0.15(0.1-0.4);3.0;n=71	0.16(0.08-0.38);3.0;n=73	0.831
Monocyte, x10^9/L	0.5(0.4-0.7);3.7;n=6434	0.5(0.36-0.6);6.09;n=9530	0.9419
Neutrophil, x10^9/L	4.8(3.61-6.9);72.38;n=6431	4.4(3.3-6.2);40.5;n=9513	0.3612
White blood count, x10^9/L	7.5(6.13-9.36);145.2;n=11978	7.1(5.8-8.8);6100.0;n=18851	0.1782
Mean cell haemoglobin, pg	30.9(29.6-32.0);44.1;n=11927	30.4(29.0-31.5);46.6;n=18775	0.9056
Myelocyte, x10^9/L	0.18(0.105-0.45);1.62;n=67	0.17(0.09-0.38);3.95;n=76	0.8561
Platelet, x10^9/L	223.0(184.0-268.0);1020.0;n=11977	244.0(203.0-290.5);1745.0;n=18846	<0.0001***
Reticulocyte, x10^9/L	55.08(35.3-80.5);324.0;n=429	55.4(39.2-80.8);460.0;n=639	0.9122
Red blood count, x10^12/L	4.61(4.2-4.99);7.95;n=11912	4.27(3.95-4.58);7.08;n=18763	0.8967
Hematocrit, L/L	0.41(0.38-0.44);0.61;n=10669	0.38(0.35-0.4);0.561;n=17300	0.7671
Biochemical tests			
K/Potassium, mmol/L	4.2(3.9-4.5);10.0;n=17388	4.2(3.81-4.5);13.3;n=25177	0.9176
Urate, mmol/L	0.42(0.343-0.5);1.12;n=5009	0.35(0.28-0.431);1.395;n=6173	0.5651
Albumin, g/L	41.5(39.0-44.0);58.0;n=14593	41.2(39.0-43.6);58.0;n=21232	0.9165
Na/Sodium, mmol/L	140.0(138.2-142.0);166.09;n=17431	141.0(139.0-142.0);181.0;n=25240	0.9249

Urea, mmol/L	6.0(5.0-7.3);60.9;n=17411	5.5(4.5-6.8);53.4;n=25207	0.0145*
Protein, g/L	73.1(70.0-77.0);112.0;n=14523	74.0(71.0-78.0);147.0;n=21127	0.8934
Creatinine, umol/L	99.0(88.0-113.0);1957.0;n=17525	77.0(68.0-89.0);1274.0;n=25396	<0.0001***
Alkaline Phosphatase, U/L	78.0(65.0-95.0);3275.0;n=12528	78.0(63.0-96.0);4280.0;n=18090	0.9123
Aspartate Transaminase, U/L	22.0(18.0-30.0);5110.0;n=3642	21.0(17.0-27.0);2148.0;n=5229	0.4564
Alanine Transaminase, U/L	22.0(16.0-33.0);3909.0;n=10498	18.0(13.0-26.0);1576.0;n=15831	0.0023**
Bilirubin, umol/L	10.2(7.9-14.0);608.0;n=12667	9.0(6.6-12.0);669.0;n=18274	0.1562
Diabetes mellitus and lipid tests			
Triglyceride, mmol/mol	1.44(1.0-2.08);25.77;n=8635	1.41(1.01-2.04);30.3;n=12504	0.8926
LDL, mmol/mol	3.2(2.6-3.8);7.92;n=6359	3.3(2.7-3.9);9.42;n=8969	0.6721
HDL, mmol/mol	1.18(1.01-1.39);4.14;n=6652	1.37(1.16-1.63);3.29;n=9338	0.0104*
HbA1c, g/dL	13.6(11.5-14.8);19.5;n=10501	12.5(11.1-13.4);18.1;n=16601	0.1551
Cholesterol, mmol/L	5.13(4.5-5.8);13.03;n=8698	5.4(4.7-6.09);13.84;n=12597	0.8723
Glucose, mmol/L	6.0(5.2-7.6);72.5;n=12819	5.8(5.1-7.5);54.3;n=18668	0.751
Diastolic blood pressure measures			
Number of tests	7(5-12);31;n=29333	7(6-11);35;n=45522	0.9012
Baseline, mm Hg	74(69-85);140.0;n=29333	79(65-89);137.0;n=45522	0.1923
Latest, mm Hg	73(66-81);140.0;n=29333	70(63-79);144.0;n=45522	0.8723
Maximum, mm Hg	82(78-94);150.0;n=29333	89(75-98);144.0;n=45522	0.0145*
Minimal, mm Hg	65(57-73);140.0;n=29333	61(54-70);128.0;n=45522	0.1261
Mean, mm Hg	75(69-81);140.0;n=29333	72(66.3-78);128.0;n=45522	0.7862
Median, mm Hg	75(69-81);140.0;n=29333	72(66-78);128.0;n=45522	0.4523
Variance	53.8(31.62-84.52);882.0;n=23964	56.6 (32.9-85.2);1152.0;n=37682	0.5621
SD	7.3(5.6-9.2);29.7;n=23964	7.5 (5.7-9.2);33.9;n=37682	0.8723
RMS	75.4(69.4-81.3);140.0;n=29333	72.4(66.7-78.3);128.0;n=45522	0.6778
CV	0.09(0.07-0.13);0.33;n=23964	0.099(0.07-0.12);0.4;n=37682	0.9561
Variability score	55.2(45.5-66.7);94.12;n=23964	56.25(47.76-66.67);95.46;n=37682	0.6241
Systolic blood pressure measures			

Number of tests	7(5-12);33;n=29333	8(5-11);34;n=45522	0.8923
Baseline, mm Hg	131(123-152);244.0;n=29333	139(120-159);251.0;n=45522	0.0132*
Latest, mm Hg	133(121-146);237.0;n=29333	135(120-146);261.0;n=45522	0.2173
Maximum, mm Hg	156(140-170);249.0;n=29333	157(138-173);274.0;n=45522	0.7671
Minimal, mm Hg	117(106-130);237.0;n=29333	114(104-128);242.0;n=45522	0.8921
Mean, mm Hg	135.96(126.5-145.5);237.0;n=29333	135.4(125-145);242.0;n=45522	0.9016
Median, mm Hg	135.5(126-145.5);237.0;n=29333	135(124-145);242.0;n=45522	0.9156
Variance	165.7(94.4-272.2);4133.3;n=23964	167.7(97.0-271.4);5618.0;n=37682	0.8723
SD	12.9(9.7-16.5);64.3;n=23964	12.95(9.9-16.5);74.95;n=37682	0.8912
RMS	136.5(127.0-146.1);237.0;n=29333	136.0(125.3-145.6);242.0;n=45522	0.9015
CV	0.09(0.07-0.1);0.3;n=23964	0.09(0.07-0.11);0.35;n=37682	0.9156
Variability score	69.2(55.7-77.8);96.7;n=23964	70.0(57.1-77.8);96.97;n=37682	0.8954

Table 2. Univariate predictors of dementia diseases for all patients, males, and females.
* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

	All patients HR[95% CI]	**P value**	**Males HR[95% CI]**	**P value**	**Females HR[95% CI]**	**P value**
Demographics						
Male gender	0.88[0.83,0.95]	0.0005***	-	-	-	-
Age, years						
[30,40]	0.02[0.01, 0.05]	<0.0001***	0.016[0.002, 0.12]	<0.0001***	0.014[0.004, 0.06]	<0.0001***
[40,50]	0.07[0.05,0.091]	<0.0001***	0.08[0.05, 0.14]	<0.0001***	0.06[0.04, 0.09]	<0.0001***
[50,60]	0.199[0.17, 0.23]	<0.0001***	0.27[0.21, 0.34]	<0.0001***	0.17[0.1, 0.2]	<0.0001***
[60,70]	1.2[1.1, 1.8]	<0.0001***	1.15[1.02, 1.3]	<0.0001***	1.4[1.1, 2.1]	<0.0001***
[70,80]	2.6[2.4, 2.8]	<0.0001***	2.3[2.02, 2.5]	<0.0001***	3.3[2.6, 4.2]	<0.0001***
[80,90]	3.3[3.1, 3.6]	<0.0001***	2.9[2.5, 3.4]	<0.0001***	4.6[3.2, 5.0]	<0.0001***
90+	2.1[1.7, 2.59]	<0.0001***	1.7[1.1, 2.5]	0.0169*	3.1[1.8, 4.1]	<0.0001***
Comorbidities						
Cardiovascular	1.9[1.8,2.1]	<0.0001***	1.5[1.4,1.7]	<0.0001***	2.2[2.0,2.4]	<0.0001***
Respiratory	3.8[3.5,4.1]	<0.0001***	4.2[3.7,4.9]	<0.0001***	3.8[3.4,4.1]	<0.0001***
Renal	1.6[1.5,1.7]	<0.0001***	1.4[1.2,1.6]	<0.0001***	1.8[1.6,2.0]	<0.0001***
Endocrine	0.7[0.6,0.8]	0.0002***	0.6[0.5, 0.9]	0.005**	0.7[0.6,0.9]	0.0116*
Diabetes mellitus	1.3[1.2,1.4]	<0.0001***	1.1[0.9,1.2]	0.452	1.4[1.2,1.5]	<0.0001***
Hypertension	1.7[1.6,1.9]	<0.0001***	1.6[1.4,1.8]	<0.0001***	1.8[1.7,2.2]	<0.0001***
Gastrointestinal	1.6[1.5,1.8]	<0.0001***	1.5[1.4,1.7]	<0.0001***	1.7[1.6,1.9]	<0.0001***
Stroke	1.9[1.8,2.0]	<0.0001***	1.6[1.4,1.8]	<0.0001***	2.2[2.0,2.3]	<0.0001***
Medications						
ACEI	1.3[1.2,1.5]	<0.0001***	1.1[0.9,1.2]	0.362	1.6[1.4,1.7]	<0.0001***
ARB	1.1[0.7,1.7]	0.687	1.3[0.7,2.7]	0.427	1.0[0.6,1.7]	0.934
Calcium channel blockers	1.4[1.3,1.5]	<0.0001***	1.2[1.1,1.3]	0.004**	1.6[1.4,1.7]	<0.0001***
Beta blockers	1.1[1.0, 1.2]	0.0036**	1.0[0.9,1.13]	0.94	1.2[1.1,1.3]	0.0002***

Diuretics for heart failure	1.9[1.7, 2.1]	<0.0001***	1.7[1.4,2.1]	<0.0001***	2.0[1.7,2.3]	<0.0001***
Diuretics for hypertension	1.3[1.2,1.4]	<0.0001***	1.08[0.9,1.3]	0.335	1.4[1.2,1.5]	<0.0001***
Nitrates	1.7[1.5,1.8]	<0.0001***	1.4[1.2,1.6]	<0.0001***	1.9[1.7,2.1]	<0.0001***
Antihypertensive drugs	1.6[1.5,1.7]	<0.0001***	1.8[1.6,2.0]	<0.0001***	1.6[1.4,1.8]	<0.0001***
Antidiabetic drugs	1.2[1.1,1.4]	<0.0001***	1.1[0.9,1.3]	0.377	1.3[1.2,1.5]	<0.0001***
Statins and fibrates	1.1[0.99,1.2]	0.0516.	0.9[0.8,1.1]	0.294	1.2[1.1,1.4]	0.002**
Complete blood count tests						
Mean corpuscular volume, fL	1.02[1.01,1.03]	<0.0001***	1.01[0.99,1.02]	0.0983.	1.03[1.02,1.03]	<0.0001***
Basophil, x10^9/L	0.4[0.1,1.6]	0.186	0.26[0.02,2.82]	0.266	0.49[0.07,3.44]	0.47
Eosinophil, x10^9/L	0.5[0.4,0.8]	0.0008***	0.5[0.3,0.8]	0.0092**	0.6[0.4,1.01]	0.0546.
Lymphocyte, x10^9/L	0.77[0.7,0.8]	<0.0001***	0.8[0.7,0.9]	0.0001***	0.75[0.7,0.8]	<0.0001***
Metamyelocyte, x10^9/L	0.9[0.2,4.1]	0.919	2.2[0.5,10.1]	0.324	0.3[0.01,7.74]	0.474
Monocyte, x10^9/L	1.5[1.2,1.7]	<0.0001***	1.1[0.8,1.5]	0.545	1.7[1.5,2.1]	<0.0001***
Neutrophil, x10^9/L	1.04[1.03,1.06]	<0.0001***	1.02[1.0,1.04]	0.0828.	1.06[1.04,1.1]	<0.0001***
White blood count, x10^9/L	1.0[0.999,1.001]	0.904	1.006[0.99,1.03]	0.559	1.00[0.99,1.001]	0.929
Mean cell haemoglobin, pg	1.04[1.02,1.06]	<0.0001***	1.02[0.99,1.05]	0.11	1.05[1.03,1.07]	<0.0001***
Myelocyte, x10^9/L	0.6[0.1,4.7]	0.662	0.001[0.001,12.5]	0.564	0.8[0.2,3.7]	0.731
Platelet, x10^9/L	0.998[0.997,0.999]	<0.0001***	0.998[0.997,0.999]	0.0014**	0.998[0.997,0.999]	0.0008***
Reticulocyte, x10^9/L	0.998[0.99,1.004]	0.522	0.99[0.98,1.001]	0.094.	1.002[0.99,1.01]	0.585
Red blood count, x10^12/L	0.65[0.6,0.69]	<0.0001***	0.67[0.6,0.74]	<0.0001***	0.62[0.56,0.68]	<0.0001***
Hematocrit, L/L	0.02[0.01,0.04]	<0.0001***	0.007[0.002,0.03]	<0.0001***	0.03[0.007,0.1]	<0.0001***
Biochemical tests						
K/Potassium, mmol/L	0.78[0.73,0.85]	<0.0001***	0.78[0.68,0.89]	0.0002***	0.8[0.72,0.88]	<0.0001***

Urate, mmol/L	0.4[0.2,0.8]	0.007**	0.14[0.04,0.44]	0.0009***	1.1[0.46,2.52]	0.859
Albumin, g/L	0.94[0.93,0.95]	<0.0001***	0.94[0.92,0.95]	<0.0001***	0.94[0.93,0.96]	<0.0001***
Na/Sodium, mmol/L	0.986[0.97,0.998]	0.0194*	0.97[0.95,0.99]	0.0015**	0.99[0.98,1.01]	0.389
Urea, mmol/L	1.05[1.04,1.06]	<0.0001***	1.02[1.01,1.04]	0.0122*	1.06[1.05,1.08]	<0.0001***
Protein, g/L	0.97[0.97,0.98]	<0.0001***	0.97[0.963,0.985]	<0.0001***	0.97[0.96,0.98]	<0.0001***
Creatinine, umol/L	1.001[1.001,1.002]	<0.0001***	1.001[0.9995,1.002]	0.273	1.003[1.002,1.003]	<0.0001***
Alkaline phosphatase, U/L	1.001[1,1.001]	0.0183*	1[0.9985,1.001]	0.964	1.001[1,1.001]	0.003**
Aspartate transaminase, U/L	0.999[0.99,1.001]	0.852	0.999[0.997,1.001]	0.53	1.001[0.999,1.002]	0.389
Alanine transaminase, U/L	0.987[0.98,0.99]	<0.0001***	0.98[0.97,0.98]	<0.0001***	0.99[0.99,1.00]	0.0012**
Bilirubin, umol/L	1.001[0.997,1.01]	0.735	1.001[0.99,1.01]	0.774	1.002[0.997,1.01]	0.474
Diabetes mellitus and lipid tests						
Triglyceride, mmol/mol	0.95[0.9,1.004]	0.0687.	0.82[0.73,0.92]	0.0007***	1.012[0.95,1.07]	0.685
LDL, mmol/mol	1.04[0.96,1.13]	0.322	0.9[0.8,1.05]	0.185	1.11[1.01,1.23]	0.039*
HDL, mmol/mol	1.2[1.02,1.5]	0.0336*	1.7[1.2,2.3]	0.002**	0.95[0.74,1.2]	0.661
HbA1c, mmol/mol	0.99[0.98,0.99]	0.002**	0.99[0.97,0.999]	0.0371*	0.98[0.97,0.998]	0.03*
Cholesterol, mmol/L	1.02[0.96,1.07]	0.58	0.92[0.84,1.01]	0.0702.	1.05[0.99,1.12]	0.126
Glucose, mmol/L	1.03[1.02,1.05]	<0.0001***	1.02[1.002,1.05]	0.0322*	1.04[1.03,1.06]	<0.0001***
Diastolic blood pressure measurements						
Number of tests	1.07[0.13,1.23]	0.8511	0.65[0.23,1.42]	0.0611	1.03[0.54,1.22]	0.1801
Baseline, mm Hg	1.15[1.11,2.34]	<0.0001***	1.43[1.01,1.76]	<0.0001***	1.24[1.01,1.93]	<0.0001***
Latest, mm Hg	1.03[1.01,1.12]	<0.0001***	1.09[1.02,1.13]	0.0045**	0.99[0.8,0.99]	0.234
Maximum, mm Hg	1.21[1.1,1.83]	<0.0001***	0.98[0.90,0.99]	0.2834	1.34[1.03,2.12]	<0.0001***
Minimal, mm Hg	0.98[0.94,0.983]	0.6523	0.97[0.92,0.98]	0.0823	0.98[0.91,0.99]	0.831
Mean, mm Hg	1.31[1.11,1.85]	<0.0001***	1.13[1.03,1.45]	<0.0001***	1.43[1.01,1.76]	<0.0001***
Median, mm Hg	1.53[1.24,3.13]	<0.0001***	1.23[1.11,2.1]	<0.0001***	1.13[1.01,1.4]	<0.0001***

Variance	1.003[1.003,1.003]	<0.0001***	1.002[1.001,1.003]	<0.0001***	1.003[1.003,1.004]	<0.0001***
SD	1.074[1.062,1.085]	<0.0001***	1.052[1.034,1.071]	<0.0001***	1.086[1.072,1.1]	<0.0001***
RMS	0.97[0.92,0.98]	0.035*	0.96[0.93,0.99]	0.2341	0.99[0.98,0.991]	0.8734
CV	58.7[69.7,194.2]	<0.0001***	11.5[5.16,19.6]	<0.0001***	13.8[4.1,39.3]	<0.0001***
Variability score	1.008[1.006,1.01]	<0.0001***	14.5[6.13,17.9]	<0.0001***	13.9[4.4,32.1]	<0.0001***
Systolic blood pressure measurements						
Number of tests	0.87[0.13,1.23]	0.2315	0.95[0.63,1.02]	0.1956	0.73[0.34,1.51]	0.8523
Baseline, mm Hg	1.011[1.01,1.012]	<0.0001***	1.006[1.003,1.009]	<0.0001***	1.014[1.012,1.015]	<0.0001***
Latest, mm Hg	1.008[1.006,1.01]	<0.0001***	1.003[1.001,1.006]	0.0157*	1.01[1.008,1.012]	<0.0001***
Maximum, mm Hg	1.011[1.01,1.013]	<0.0001***	1.008[1.006,1.01]	<0.0001***	1.013[1.011,1.015]	<0.0001***
Minimal, mm Hg	1.005[1.003,1.007]	<0.0001***	1.001[0.9978,1.004]	0.615	1.008[1.005,1.01]	<0.0001***
Mean, mm Hg	1.016[1.014,1.018]	<0.0001***	1.009[1.006,1.013]	<0.0001***	1.02[1.018,1.022]	<0.0001***
Median, mm Hg	1.016[1.014,1.018]	<0.0001***	1.009[1.005,1.012]	<0.0001***	1.02[1.017,1.022]	<0.0001***
Variance	1.001[1.001,1.001]	<0.0001***	1.001[1.001,1.001]	<0.0001***	1.001[1.001,1.001]	<0.0001***
SD	1.052[1.047,1.057]	<0.0001***	1.042[1.034,1.051]	<0.0001***	1.057[1.051,1.063]	<0.0001***
RMS	1.017[1.015,1.019]	<0.0001***	1.01[1.006,1.013]	<0.0001***	1.021[1.018,1.023]	<0.0001***
CV	44.4[18.6,105.9]	<0.0001***	10.5[2.5,44.8]	<0.0001***	10.3[3.5,30.8]	<0.0001***
Variability score	1.009[1.007,1.012]	<0.0001***	1.009[1.005,1.013]	<0.0001***	1.01[1.007,1.012]	<0.0001***

Table 3. Multivariate predictors of dementia diseases for all patients, males, and females
* for p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001

	All patients HR[95% CI]	P value	Males HR[95% CI]	P value	Females HR[95% CI]	P value
Demographics						
Male gender	0.88[0.62, 1.27]	0.5051	-	-	-	-
Age						
[30,40]	-	-	-	-	1.05[1.01,1.37]	0.0035**
[40,50]	1.05[1.01, 1.26]	0.0003 ***	-	-	1.03[1.01,1.12]	<0.0001***
[50,60]	1.17[1.06, 1.45]	0.0004 ***	-	-	1.09[1.04,1.20]	<0.0001***
[60,70]	1.43[1.20, 1.93]	0.0011 **	1.23[1.04,1.31]	<0.0001***	1.42[1.24,1.72]	<0.0001***
[70,80]	1.45[1.36, 1.93]	<0.0001***	-	-	1.28[1.11,1.81]	<0.0001***
[80,90]	1.47[1.09, 3.06]	<0.0001***	1.18[1.01,1.52]	<0.0001***	1.27[1.06,2.11]	<0.0001***
90+	1.21[0.41, 3.57]	0.7316	-	-	1.67[1.15,3.28]	<0.0001***
Comorbidities						
Cardiovascular	1.10[1.08, 1.55]	<0.0001***	1.03[0.32, 3.32]	0.9629	1.07[1.04,1.37]	<0.0001***
Respiratory	1.56[1.05, 2.31]	0.0275 *	1.71[0.48, 6.10]	0.4095	1.59[1.22,2.07]	0.0006***
Renal	0.84[0.60, 1.18]	0.3239	2.08[0.76, 5.69]	0.156	0.79[0.62,1.02]	0.0688.
Endocrine	1.26[1.09, 1.71]	0.0089 **	-	-	-	-
Diabetes mellitus	1.27[0.86, 1.87]	0.2260	-	-	1.48[1.13,1.94]	0.0049**
Hypertension	1.21[1.09, 1.46]	<0.0001***	1.05[1.03, 4.76]	<0.0001***	1.24[1.15,1.61]	<0.0001***
Gastrointestinal	1.66[1.23, 2.23]	0.0009 ***	2.80[0.99, 7.89]	0.0513.	1.36[1.10,1.67]	0.0043**
Stroke	0.95[0.69, 1.31]	0.7431	1.35[0.44, 4.14]	0.6017	1.13[1.02,1.43]	<0.0001***
Medications						
ACEI	0.93[0.66, 1.30]	0.6554	-	-	0.84[0.65,1.07]	0.1618
Calcium channel blockers	1.15[1.04, 1.57]	<0.0001***	0.86[0.30, 2.45]	0.7769	1.21[1.05,1.41]	<0.0001***
Beta blockers	1.06[0.77, 1.46]	0.7140	-	-	1.04[0.83,1.31]	0.7449

Diuretics for heart failure	0.84[0.54, 1.33]	0.4671	0.77[0.13, 4.66]	0.7772	1.23[1.05,1.61]	<0.0001***
Diuretics for hypertension	1.01[1.01, 1.44]	<0.0001***	-	-	1.18[1.02,1.55]	<0.0001***
Nitrates	0.75[0.51, 1.11]	0.1499	0.74[0.24, 2.30]	0.6071	1.24[1.17,1.45]	<0.0001***
Antihypertensive drugs	1.06[0.74, 1.50]	0.7566	2.20[0.76, 6.32]	0.1439	0.92[0.66,1.29]	0.6351
Antidiabetic drugs	0.94[0.64, 1.39]	0.7661	-	-	0.96[0.73,1.27]	0.7745
Statins and fibrates	-	-	-	-	0.86[0.66,1.13]	0.2883
Complete blood count tests						
Mean corpuscular volume, fL	0.98[0.89, 1.07]	0.5890	-	-	1.21[1.04,1.67]	<0.0001***
Eosinophil, x10^9/L	1.28[1.10, 1.77]	0.0138 *	0.61[0.06, 6.42]	0.6803	-	-
Lymphocyte, x10^9/L	1.03[0.96, 1.11]	0.3769	1.28[0.59, 2.78]	0.5312	0.99[0.87,1.12]	0.8179
Monocyte, x10^9/L	0.66[0.36, 1.21]	0.1808	-	-	1.11[1.07,1.59]	<0.0001***
Neutrophil, x10^9/L	1.03[1.08, 1.47]	<0.0001***	-	-	1.22[1.09,1.53]	<0.0001***
Mean cell haemoglobin, pg	0.99[0.82, 1.20]	0.9334	-	-	0.96[0.84,1.10]	0.5891
Platelet, x10^9/L	1.00[1.00, 1.00]	0.3739	1.00[0.99, 1.01]	0.5299	1.00[1.00,1.00]	0.6566
Red blood count, x10^12/L	0.53[0.18, 1.57]	0.2488	0.82[0.22, 3.05]	0.7632	0.66[0.25,1.69]	0.3824
Hematocrit, L/L	-	-	-	-	35.71[0.00,191.00]	0.5199
Biochemical tests						
K/Potassium, mmol/L	0.84[0.65, 1.08]	0.1703	0.58[0.55, 1.24]	0.2612	0.96[0.79,1.15]	0.6261
Urate, mmol/L	1.14[1.04, 1.53]	0.0037 **	0.60[0.01, 35.17]	0.8035	-	-
Albumin, g/L	0.99[0.95, 1.03]	0.6981	0.91[0.77, 1.07]	0.2497	1.03[0.99,1.06]	0.1187
Urea, mmol/L	0.98[0.91, 1.05]	0.4914	-	-	1.17[1.03,1.72]	<0.0001***
Na/Sodium, mmol/L	-	-	1.10[0.94, 1.30]	0.2317	-	-
Protein, g/L	1.03[1.00, 1.06]	0.0543.	1.13[1.01, 1.26]	0.0623.	0.99[0.97,1.01]	0.4858

Creatinine, umol/L	1.00[0.99, 1.01]	0.9421	-	-	1.00[1.00,1.01]	<0.0001***
Aspartate transaminase, U/L	0.99[0.97, 1.00]	0.0166*	0.96[0.91, 1.01]	0.0833.	1.00[1.00,1.00]	0.7237
Alanine transaminase, U/L	-	-	-	-	1.00[1.00,1.00]	0.9126
Diabetes mellitus and lipid tests						
Triglyceride, mmol/mol	-	-	1.22[0.66, 2.26]	0.5324	-	-
HDL, mmol/mol	-	-	2.73[0.78, 9.52]	0.1161	-	-
Glucose, mmol/L	1.02[0.99, 1.06]	0.2476	-	-	1.01[0.97,1.04]	0.6423
Diastolic blood pressure measurements						
Baseline, mm Hg	1.14[1.07, 1.52]	<0.0001***	1.15[1.08, 1.43]	<0.0001***	1.21[1.02,1.21]	<0.0001***
Latest, mm Hg	1.00[0.98, 1.02]	0.1834	1.06[0.99, 1.12]	0.0816.	-	-
Maximum, mm Hg	1.01[0.96, 1.05]	0.8364	-	-	1.19[1.06,1.92]	<0.0001***
Mean, mm Hg	1.25[1.14, 1.57]	<0.0001***	0.87[0.65, 1.17]	0.366	1.32[1.12,1.79]	<0.0001***
Median, mm Hg	1.04[0.96, 1.13]	0.3311	1.23[1.01, 1.32]	<0.0001***	1.02[0.96,1.08]	0.4816
Variance	1.4[1.04, 1.51]	<0.0001***	1.3[1.07, 1.94]	<0.0001***	1.11[1.01,1.32]	<0.0001***
SD	1.29[0.97, 1.72]	0.0800.	1.52[0.37, 6.16]	0.5582	0.96[0.79,1.17]	0.6825
CV	1.31[1.02, 1.65]	<0.0001***	0.00[0.00, 12.00]	0.5327	-	-
Variability score	1.22[1.09, 2.11]	<0.0001***	1.19[1.05, 1.83]	<0.0001***	1.22[1.12,2.41]	<0.0001***
Systolic blood pressure measurements						
Baseline, mm Hg	1.02[1.01, 1.21]	<0.0001***	1.03[0.99, 1.07]	0.1789	1.31[1.09,2.34]	<0.0001***
Latest, mm Hg	1.01[1.00, 1.02]	0.1029	-	-	1.00[1.00,1.01]	0.3566
Maximum, mm Hg	1.40[1.18, 1.42]	<0.0001***	1.00[0.94, 1.06]	0.9429	1.02[1.01,1.03]	<0.0001***
Minimal, mm Hg	1.02[0.99, 1.05]	0.2281	-	-	1.02[1.00,1.05]	0.0322*
Mean, mm Hg	1.27[1.17, 1.61]	<0.0001***	0.00[0.00, 10.33]	0.1196	0.71[0.27,1.84]	0.4817
Median, mm Hg	1.00[0.95, 1.04]	0.9105	0.94[0.82, 1.08]	0.399	1.03[1.00,1.07]	<0.0001***

Variance	1.00[0.99, 1.00]	0.1617	0.98[0.94, 1.02]	0.251	1.15[1.01,1.42]	<0.0001***
SD	1.18[1.01, 1.69]	<0.0001***	1.86[0.48, 7.22]	0.3698	0.98[0.85,1.12]	0.7148
RMS	3.69[0.98, 13.81]	0.0529.	-	-	1.31[1.11,3.35]	<0.0001***
CV	-	-	0.00[0.00, 12.00]	0.2279	-	-
Variability score	1.43[1.18, 1.91]	<0.0001***	1.03[0.98, 1.08]	0.2033	1.32[1.09,2.11]	<0.0001***

Table 4. Clinical risk scores for early prediction of dementia diseases in male (left) and female (right) patients

Clinical Risk Score for Males			**Clinical Risk Score for Females**		
Risk factors	**Score**	**Cut-off**	**Risk factors**	**Score**	**Cut-off**
Age			Age of first BP		
[60,70]	1.23	Present	[30,40]	1.05	Present
[80,90]	1.18	Present	[40,50]	1.03	Present
Prior hypertension	1.05	Present	[50,60]	1.09	Present
High diastolic BP baseline, mm Hg	1.15	75.5 mm Hg	[60,70]	1.42	Present
High diastolic BP median, mm Hg	1.23	73.2 mm Hg	[70,80]	1.28	Present
High diastolic BP variance	1.3	67.4	[80,90]	1.27	Present
High diastolic BP variability score	1.19	59.2	90+	1.67	Present
High systolic BP median, mm Hg	1.01	141.5 mm Hg	Prior cardiovascular	1.07	Present
High systolic BP variance	1.01	235.4	Prior respiratory	1.59	Present
			Prior diabetes mellitus	1.48	Present
			Prior hypertension	1.24	Present
			Prior gastrointestinal	1.36	Present
			Prior stroke	1.13	Present
			High mean corpuscular volume, fL	1.21	92.4 fL
			High monocyte, x10^9/L	1.11	0.53 x10^9/L
			High neutrophil, x10^9/L	1.22	5.3 x10^9/L

	High urea, mmol/L	1.17	6.5 mmol/L
	High creatinine, umol/L	1.00	102.4 umol/L
	High diastolic BP baseline, mm Hg	1.21	77.2 mm Hg
	High diastolic BP maximum, mm Hg	1.19	79.1 mm Hg
	High diastolic BP mean, mm Hg	1.32	75.5 mm Hg
	High diastolic BP variance	1.11	69.8
	High diastolic BP variability score	1.22	68.5
	High systolic BP baseline, mm Hg	1.31	145.2 mm Hg
	High systolic BP maximum, mm Hg	1.01	169.3 mm Hg
	High systolic BP median, mm Hg	1.03	149.5 mm Hg
	High systolic BP variance	1.15	245.1
	High systolic BP RMS	1.31	149.23
	High systolic BP variability score	1.32	0.13

Table 5. Simplified clinical risk scores for early prediction of dementia diseases in male (left) and female (right) patients after excluding BP variability measures

Clinical Risk Score for Males			**Clinical Risk Score for Females**		
Risk factors	**Score**	**Cut-off**	**Risk factors**	**Score**	**Cut-off**
Age			Age of first BP		
[60,70]	1.33	Present	[30,40]	1.04	Present
[80,90]	1.28	Present	[40,50]	1.07	Present
Prior hypertension	1.05	Present	[50,60]	1.06	Present
Lower alanine transaminase, U/L	0.96	23.2 U/L	[60,70]	1.42	Present
Hematocrit, L/L	0.23	0.45 L/L	[70,80]	1.31	Present
High diastolic BP baseline, mm Hg	1.21	75.4mm Hg	[80,90]	1.25	Present
			90+	2.15	Present
			Prior cardiovascular	1.06	Present
			Prior respiratory	1.61	Present
			Prior diabetes mellitus	1.52	Present
			Prior hypertension	1.43	Present
			Prior stroke	1.82	Present
			High mean corpuscular volume, fL	1.23	94.1 fL
			High monocyte, x10^9/L	1.19	0.53 x10^9/L
			High neutrophil, x10^9/L	1.24	5.2 x10^9/L
			High urea, mmol/L	1.21	6.6 mmol/L
			High diastolic BP baseline, mm Hg	1.32	77.5 mm Hg
			High systolic BP baseline, mm Hg	1.28	143.2 mm Hg

Table 6. Five-fold cross validation for the comparisons between gender-specific clinical risk scores with BP variabilities and simplified clinical risk scores without BP variabilities for early prediction of dementia diseases.

Systems for males	**Cut-off**	**C-index**
Scoring system considering BP variabilities	4.48	0.9082
Simplified scoring system without BP variabilities	4.32	0.8201
Systems for females	**C-index**	**Cut-off**
Scoring system considering BP variabilities	11.12	0.9123
Simplified scoring system without BP variabilities	17.23	0.8161

Figure legends

Figure 1. Age-specific incidence of dementia diseases between male patients and female patients.

Figure 2. Survival curves of dementia outcome in the overall cohort, male cohort, and female cohort.

Figure 3. Discrimination performance of clinical risk scores for male (top) and female (bottom) patients.