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Visit-to-visit variability in multiple biological measurements and cognitive performance and risk of cardiovascular disease: A cohort study

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ABSTRACT

Background: Visit-to-visit variability in single biological measurements has been associated with cognitive decline and an elevated risk of cardiovascular diseases (CVD). However, the effect of visit-to-visit variability in multiple biological measures is underexplored. We investigated the effect of visit-to-visit variability in blood pressure (BP), heart rate (HR), weight, fasting plasma glucose, cholesterol, and triglycerides on cognitive performance and CVD.

Methods: Data on BP, HR, weight, glucose, cholesterol, and triglycerides from study visits in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial were used to estimate the association between visit-to-visit variability, cognitive performance (Mini Mental State Examination (MMSE) score) and CVD (non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death). Visit-to-visit variation for each measurement was estimated by calculating each individuals visit-to-visit standard deviation for that measurement. Participants whose standard deviation was in the highest quarter were classified as having high variation. Participants were grouped into those having 0, 1, 2, 3, or $\geq$ 4 high variation measurements. Regression and survival models were used to estimate the association between biological measures with MMSE and CVD with adjustment for confounders and mean measurement value.

Results: After adjustment for covariates, higher visit-to-visit variability in BP, HR, weight, and FPG were associated with poorer MMSE and a higher risk of CVD. Effect sizes did not vary greatly by measurement. The effects of high visit-to-visit variability were additive; compared to participants who had no measurements with high visit-to-visit variability, those who had high visit-to-visit variability in $\geq$4 measurements had poorer MMSE scores (-0.63 (95 % CI -0.96 to -0·31). Participants with $\geq$4 measurements with high visit-to-visit variability compared to participants with none had higher risk of CVD (hazard ratio 2.46 (95 % CI 1.63 to 3.70).

Conclusion: Visit-to-visit variability in several measurements were associated with cumulatively poorer cognitive performance and a greater risk of CVD.

1. Introduction

People with higher visit-to-visit variability in systolic blood pressure (SBP), heart rate, cholesterol, body weight, and glucose levels have a higher risk of cognitive decline, stroke, and heart attack, independent of mean levels.[1–9] Variability in these and other measurements has been

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associated with poorer health.[10–13] However, the cumulative effect of variability in multiple measurements and their relationship to several health outcomes has seldom been reported. We found two studies with the outcomes of cognition or dementia[14,15] and three studies of cardiovascular disease[8,16,17] all of which found worse outcomes with a greater number of high-variability parameters. These five studies were performed in homogenous populations within one or two countries, and most were from cohorts or electronic health records, which tend to have poorer quality data than randomised controlled trials.

Causal explanations for poorer health with higher visit-to-visit variability include baroreceptor dysfunction, progression of vessel atheroma and stiffening, or fluctuations in endothelial or autonomic function.[18] However, non-causal explanations are also plausible. Visit-to-visit variability does not show specificity to cardiovascular outcomes; e.g. depression is associated with variability in waist circumference, blood pressure, glucose, high-density lipoprotein cholesterol and triglyceride levels.[10] Reverse causality is plausible, because visit-to-visit variability may be caused by stroke or heart attack, [1] or may be a consequence of Alzheimer's disease pathology.[2]

Lastly, visit-to-visit variability in biological measurements may be a marker of frailty.[19–21] Frailty is the age-related decline in health due to reduced homeostatic reserve, which decreases ability to respond to stressors.[22] High levels of visit-to-visit variability may indicate overall poorer homeostatic regulation.[23,24] If this is the case, we might expect visit-to-visit variability in one measurement to be related to variability in others, and for the magnitude of the effect of visit-to-visit variability in different biological measurements to be broadly similar.

In this study we used data from the Outcome Reduction with Initial Glargine Intervention (ORIGIN)[25] trial to estimate the associations between visit-to-visit variability in multiple biological measures, with cognitive performance and cardiovascular disease (CVD). We investigated whether visit-to-visit variability in these measurements was correlated, whether the effect sizes were similar across different measurements, and whether the effects of high visit-to-visit variability in multiple measurements on cognitive performance or risk of CVD was cumulative.

2. Material and methods

2.1. Population

We used data from the ORIGIN trial, coordinated by the Population Health Research Institute (PHRI), Canada.[25] The design and results of ORIGIN have been described in detail previously.[25] Briefly 12,537 participants aged 50 years or older with dysglycemia, who had additional cardiovascular risk factors were recruited from 573 sites across 40 countries. Participants were randomised to either titrated basal insulin glargine, targeting a fasting plasma glucose concentration of <95 mg/dl (5·3 mmol/L) or lower, or standard care, and to either n-3 fatty acid (1 g) or placebo, with the use of a 2-by-2 factorial design. Ethical approval was granted by the review boards of all the participating institutions, and all participants provided written informed consent. Supplementary Table 1 summarises trial characteristics.

2.2. Outcomes

We considered two outcomes: global cognitive performance, and in-trial cardiovascular events (non-fatal stroke, non-fatal myocardial infarction (MI), or cardiovascular death, as per the primary outcome of the ORIGIN study[25]). We counted only the first occurrence of a cardiovascular event during trial. We used end-of-study Mini-Mental State Examination (MMSE) scores to measure cognitive performance. A paper version of the MMSE was administered in person by site staff at baseline, year 2, year 4 and trial end. To account for baseline cognitive scores, only participants with MMSE at baseline and at least one other time point were included. We used participants' last available MMSE score as the outcome.

2.3. Exposures

We measured visit-to-visit variability in systolic blood pressure (SBP; mmHg), heart rate (HR; beats per minute), fasting plasma glucose (FPG; mmol/L), total cholesterol (mmol/L), triglycerides (mmol/L), and weight (kg). Supplementary Table 2 shows the number of time points for each measurement, predominantly taken at randomisation, annually, and again at end of study. We chose within-person standard deviation (SD) as a measure of variability in our analysis for ease of calculation. Evidence suggests that the method used to measure variability minimally affects results.[8,14,15] For each biological measurement, visit-to-visit variability was the SD of a participant's values over time, excluding participants who had fewer than 3 time points for that specific measurement. To compare variability in biological measurements, we standardised each measurement's variability to its normal distribution. We expressed this in z-scores (i.e., SD units above or below the mean variability). This process ensures a comparable and standardised assessment of variability across the various biological measurements, where the mean variability for each measurement is 0, with z-scores indicating how far a given data point lies above or below that mean. As the introduction of insulin in people randomly assigned to this intervention would have affected fasting plasma glucose levels, we excluded values measured in the first twelve weeks for all participants.

We identified participants whose Z-score for each measurement was in the top 25 %. Participants were assigned a value of 1 for each measurement they had in the highest quarter; these values were summed over six measurements, which we analysed in groups 0, 1, 2, 3, ≥4. We only included participants who had a measure of variability for all 6 measures in this analysis (Fig. 1).

2.4. Covariates

Covariates measured at baseline were age, sex, education of greater than 12 years, baseline MMSE score (as cognitive status is a predictor of both later cognitive decline and risk of CVD), current smoking status, treatment allocation, and self-reported or investigator-reported hypertension, diabetes, and prior stroke or MI. In analysis where weight variability was not included in the model, we additionally added BMI as a covariate. We also controlled for the non-standardised mean measurement value of the explanatory measurement in the individual variability analysis (mean SBP, HR etc.), and the non-standardised mean values of all six measurements in the analyses of 'high variability' across multiple measurements. Finally, we controlled for time from baseline until final MMSE in the analysis of cognitive performance.

2.5. Statistical analyses

First, we used linear regression to examine the relationship between our dependent variable, participants' final MMSE score, and our exposure variable, visit-to-visit variability (expressed as continuous Z-scores) across six measurements. Subsequently, we estimated the mean difference in final MMSE score in participants with high visit-to-visit variability in 1, 2, 3, or 4 or more measurements, as compared to those with no measures with high variability. All cognitive analyses were adjusted for the baseline MMSE score. Third, we calculated hazard ratios (HR) for incident CVD associated with a 1-point increase in Z-score for visit-to-visit variability in each measurement. This analysis took into account the competing risk of non-CVD death using sub-distribution hazard models. Finally, we determined the hazard ratios for CVD as the dependent variable in participants with 1, 2, 3, or 4 or more measurements exhibiting high visit-to-visit variability, in comparison to those with none. As sensitivity analyses, we estimated the HRs for incident non-fatal stroke and for incident non-fatal MI separately. As a further sensitivity analysis, we used a dichotomous outcome of significant

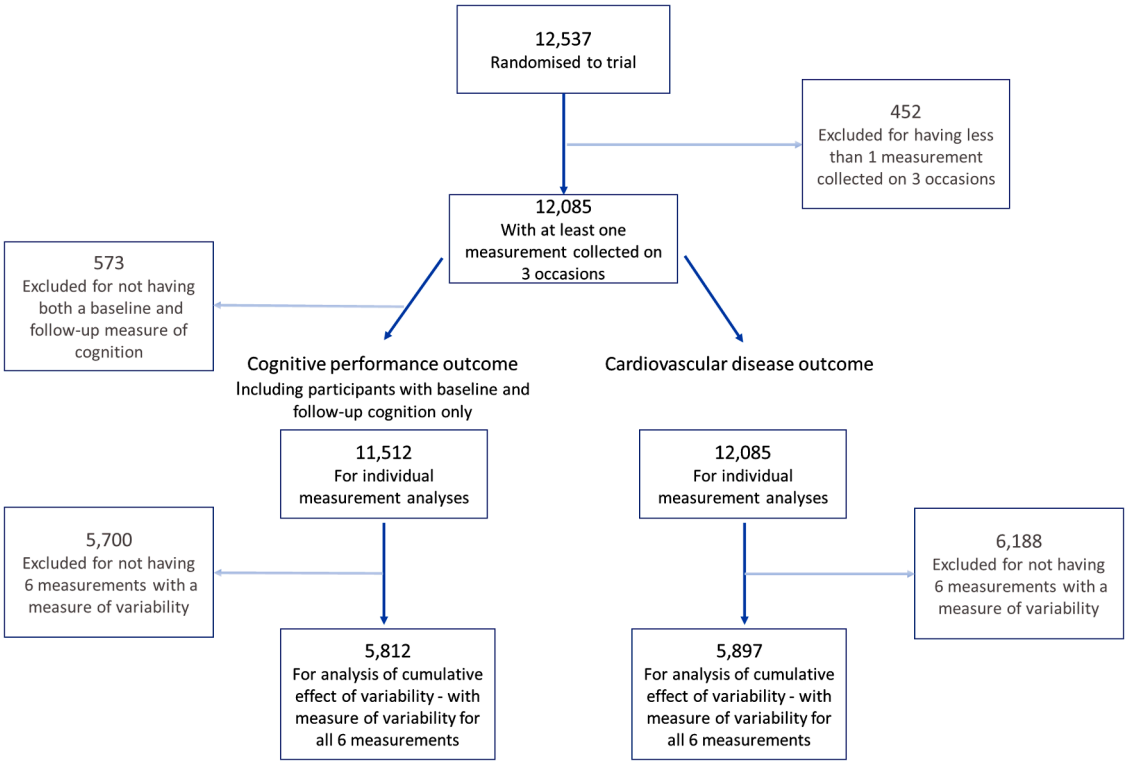

Fig. 1. Flow chart of participants included in each analysis.

cognitive impairment (defined as MMSE <24)[26] to determine the HR of end of trial cognitive impairment when accounting for baseline cognitive impairment and the competing risk of death. We analysed data in the sub-groups of age <60, 60–65, and >65, and male and female. To estimate whether high variability in one measurement was associated with high variability in the others, we calculated Pearson's correlations of the standard deviation of each of the six measurements with each other. Associations across all measurements were subsequently corrected for multiple comparisons using the Benjamini and Hochberg False Discovery Rate (FDR) correction.[27] Sensitivity analyses were carried out excluding participants who had a cardiovascular event (stroke or MI) during the trial for the cognitive performance analyses, as such events can independently affect cognition[28] and variability[29]. Statistical analyses were performed in R version 4.2.1.

3. Results

Of 12,537 participants, we excluded 452 participants without a measure of variability (SD) for at least one measurement, leaving 12,085 for analysis (Fig. 1). Eligible participants had a mean age of 64 years (SD 8), a mean BMI of 30 (SD 5), 4226 (35 %) were female, 4608 (38 %) had more than 12 years of education, and 1484 (12 %) were current smokers. At baseline, 11,871 participants (98 %) had at least one of TIA, stroke, MI, angina, or peripheral artery disease, and 8058 (67 %) had at least one of hypertension, diabetes, current smoker, elevated cholesterol or obesity (Table 1). The mean MMSE was 27·9 (SD 2·8) at baseline and 27·3 (SD 3·6) at final follow-up available (median 6.2 years). During trial follow-up, 1858 participants (15 %) had a cardiovascular event; 613 (5 %) had a stroke, 586 (5 %) had a MI and 659 (6 %) died from a cardiovascular cause (Table 2). Table 3 presents the mean measurement values, variability (SD) and standardised variability (Z-score of SD) for each measurement. The baseline characteristics of the 5897 participants who had three or more measures for all six measurements (Fig. 1) were similar to the rest of the population (data on request).

3.1. Visit-to-visit variability and cognitive performance

Following adjustment for baseline MMSE, covariates and mean measurement levels, the reduction in end of study MMSE score for a one point higher Z-score of SD was as follows: −0.11 (95 % CI −0.16 to −0.05) for weight, −0.13 (95 % CI −0.19 to −0.07) for systolic blood pressure, −0.07 (95 % CI −0.12 to −0.01) for heart rate, −0.15 (95 % CI −0.23 to −0.07) for fasting plasma glucose, −0.06 (95 % CI −0.12 to 0.00) for total cholesterol, and −0.19 (95 % CI −0.27 to −0.10) for triglycerides (Fig. 2).

When compared to participants with no Z-scores in the highest quarter (i.e., no high variability measurements), participants with 1, 2, 3, or ≥4 high variability measurements exhibited MMSE scores lower by −0.14 (95 % CI −0.33 to 0.04), −0.49 (95 % CI −0.69 to −0.29), −0.62 (95 % CI −0.88 to −0.37), and −0.63 (95 % CI −0.96 to −0.31) respectively, after adjusting for confounders and mean levels (Fig. 3). Notably, a significant trend was observed towards poorer MMSE scores with an increasing number of measurements displaying high visit-to-visit variability; MMSE scores decreased by −0.23 (95 % CI −0.29 to −0.17; ptrend<0.001) per 1 unit increase in number of high variability measurements (Fig. 3).

3.2. Visit-to-visit variability and cardiovascular disease

After accounting for the competing risk of non-CVD death, and adjusting for covariates and mean measurement levels, the adjusted hazard ratio (aHR) of CVD for a one point increase in z-score of SD was, for weight 1.08 (95 % CI 1.04 to 1.13), for systolic blood pressure 1.18 (95 % CI 1.12 to 1.25), for heart rate 1.14 (95 % CI 1.09 to 1.19), for fasting plasma glucose 1.14 (95 % CI 1.07 to 1.22), for total cholesterol 1.19 (95 % CI 1.11 to 1.27), and for triglycerides 0.97 (95 % CI 0.90 to 1.05) (Fig. 4). Analyses examining stroke and MI individually had similar aHR.

When compared with participants with zero measurements with high visit-to-visit variability, the aHR for CVD was; for people with one

Table 1
Baseline characteristics for participants who have a measure of visit-to-visit variability for at least one of the 6 outcomes.

	Low variability * (*N* = 7456)	High variability* (*N* = 4629)	Total (*N* = 12,085)
Female	2480 (33.3 %)	1746 (37.7 %)	4226 (35.0 %)
Age, Mean (SD)	63.7 (7.74)	63.0 (7.82)	63.5 (7.78)
Education > 12 years	2958 (39.7 %)	1650 (35.6 %)	4608 (38.1 %)
Current Smoker	836 (11.2 %)	648 (14.0 %)	1484 (12.3 %)
Weight (kg), Mean (SD)	82.5 (16.2)	84.8 (18.2)	83.4 (17.0)
Body Mass Index, Mean (SD)	29.5 (5.00)	30.5 (5.55)	29.9 (5.24)
Waist to hip ratio, Mean (SD)	0.952 (0.0958)	0.960 (0.105)	0.955 (0.0994)
Diastolic Blood Pressure, Mean (SD)	82.7 (11.4)	86.5 (12.7)	84.2 (12.0)
Systolic Blood Pressure, Mean (SD)	143 (19.7)	151 (23.8)	146 (21.7)
Heart rate, Mean (SD)	68.6 (11.3)	71.7 (13.2)	69.7 (12.1)
Fasting plasma glucose (FPG), Mean (SD)	7.17 (1.83)	7.58 (2.18)	7.33 (1.98)
Total cholesterol, Mean (SD)	4.75 (1.11)	5.14 (1.29)	4.90 (1.20)
Triglycerides, Mean (SD)	1.67 (0.952)	2.18 (1.53)	1.87 (1.23)
Baseline Medical History, N (%)			
Stroke	916 (12.3 %)	644 (13.9 %)	1560 (12.9 %)
Transient ischaemic attack	0 (0 %)	0 (0 %)	0 (0 %)
Myocardial infarction	2761 (37.0 %)	1489 (32.2 %)	4250 (35.2 %)
Angina	2746 (36.8 %)	1622 (35.0 %)	4368 (36.1 %)
Hypertension	5707 (76.5 %)	3890 (84.0 %)	9597 (79.4 %)
Atrial fibrillation	208 (2.8 %)	182 (3.9 %)	390 (3.2 %)
Diabetes	5987 (80.3 %)	3971 (85.8 %)	9958 (82.4 %)
Baseline Cardiovascular Risk Factors § N (%)			
0	183 (2.5 %)	31 (0.7 %)	214 (1.8 %)
1	1115 (15.0 %)	352 (7.6 %)	1467 (12.1 %)
2	2538 (34.0 %)	1297 (28.0 %)	3835 (31.7 %)
3 or more	3620 (48.6 %)	2949 (63.7 %)	6569 (54.4 %)
Baseline Cardiovascular Disease ¶ N (%)			
0	2393 (32.1 %)	1634 (35.3 %)	4027 (33.3 %)
1	3641 (48.8 %)	2150 (46.4 %)	5791 (47.9 %)
2	1320 (17.7 %)	768 (16.6 %)	2088 (17.3 %)
3 or more	102 (1.4 %)	77 (1.7 %)	179 (1.5 %)
Follow up time in years, Median (IQR)	6.1 (5.8 – 6.7)	6.2 (5.8 – 6.8)	6.2 (5.8 – 6.7)

* Low variability defined as participants with 0 or 1 measurements with high visit-to-visit variability (Z-score was in the top 25 %). High variability defined as participants with 2, 3, or 4 or more measurements with high visit-to-visit variability (Z-score was in the top 25 %).

§ Defined as the number of the following cardiovascular risk factors participants have at baseline; hypertension, diabetes, current smoker, elevated cholesterol, or obesity.

¶ Defined as the number of the following categories of cardiovascular disease participants have previously had; transient ischaemic attack (TIA), stroke, myocardial infarction (MI), angina, or peripheral artery disease. Abbreviations: N: number, SD: standard deviation.

Table 2
Cognition, and cardiovascular disease incidence for participants who have a measure of visit-to-visit variability for at least one of the 6 outcomes.

	N = 12,085
Cognition^	
MMSE score, Mean (SD)	
Baseline MMSE	27.9 (2.84)
Follow up MMSE	27.3 (3.55)
MMSE <24*, N (%)	
Baseline MMSE <24	877 (7.3 %)
Follow up MMSE <24	1377 (11.4 %)
In trial cardiovascular disease¶, N (%)	1858 (15.4 %)
Non-fatal stroke	613(5.1 %)
Non-fatal myocardial infarction	586 (4.8 %)
Cardiovascular death	659 (5.5 %)

Abbreviations: MMSE: mini-mental state examination, SD: standard deviation, N: number.

^ Cognitive data is presented for those who have both a baseline and at least one other follow up measure.

* MMSE <24 used as a marker of significant cognitive impairment.

¶ CVD defined as non-fatal stroke, non-fatal myocardial infarction (MI), or death from cardiovascular causes.

Table 3
Mean measurement values, variability (SD) and standardised variability (Z-score of SD) for each measurement.

	Mean measurement value	Variability (SD)	Standardised variability (Z-score of SD)
Weight	83.8	3.41	−0.003
Systolic Blood Pressure	139.0	13.30	0.013
Heart rate	69.8	7.03	0.010
Fasting Plasma Glucose	5.67	1.04	−0.002
Cholesterol	4.72	0.67	0.001
Triglycerides	1.74	0.55	0.001

Mean measurement value is the mean of all time points. Variability is the standard deviation (SD) of the mean measurement value. Standardised variability is the variability (SD) standardised to the normal distribution using z-scores.

measurement with high visit-to-visit variability 1.32 (95 % CI 1.00 to 1.76), two measurements 1.69 (95 % CI 1.26 to 2.26), three measurements 2.21 (95 % CI 1.59 to 3.07), and four measurements 2.46 (95 % CI 1.63 to 3.70) (Fig. 5). There was a significant trend towards a higher risk of CVD in participants with increasing numbers of measurements with high visit-to-visit variability; there was an increase in aHR of 1.23 (95 % CI 1.14 to 1.32; ptrend<0.001) per 1 unit increase in number of high variability measurements (Fig. 5). Analyses examining stroke or MI as separate outcomes were similar.

All significant p-values survived correction for FDR (Supplementary Table 3 provides FDR corrected p-values).

3.3. Correlation between variability measures

Table 4 provides Pearson's correlation coefficients for the relationship between visit-to-visit variability in the measurements. Although visit-to-visit variability in different measurements were mostly significantly correlated, the effect sizes were small and so only explain a small proportion of the variance (proportion of variance explained (R^2 *100) all below 5 % of the variance).

3.4. Sensitivity and subgroup analyses

Excluding participants who had a cardiovascular event during the trial had a very small effect on cognitive analyses.

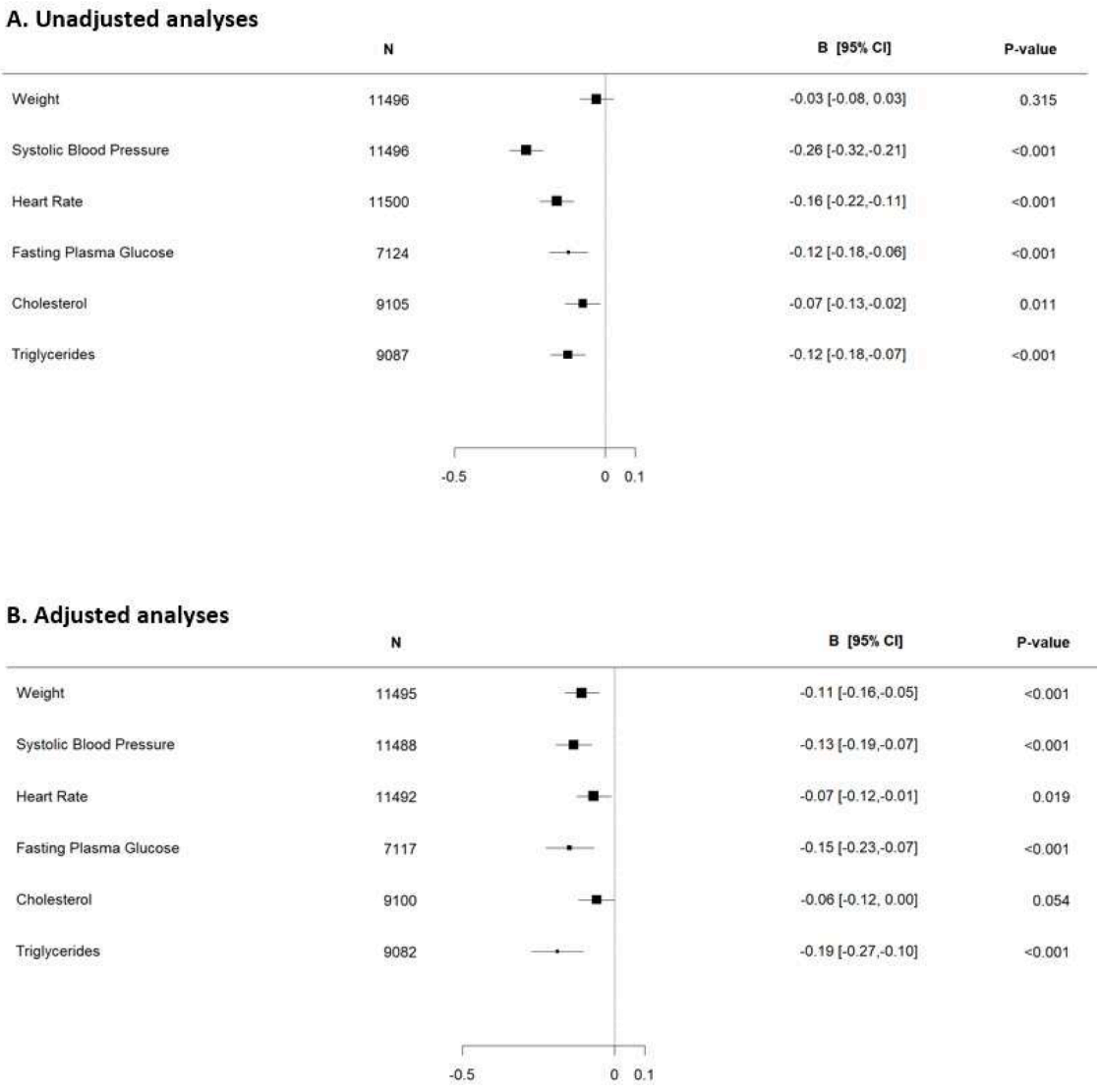

Fig. 2. MMSE score per one point increase in visit-to-visit variability for each of our six measurements; showing A. adjusted for baseline MMSE only, and B. adjusted for baseline MMSE, age, sex, education, BMI (except for in weight variability analysis), smoking status, treatment allocation, hypertension, diabetes, prior stroke, prior MI, mean measurement value, and time. Where variability is measured as the z-score of the SD (i.e., how many standard deviations above or below the mean SD each participant's value lies) for each measurement.
Abbreviations: MMSE: mini-mental state examination, N: number, B: beta, CI: confidence interval. All significant p-values survived correction for false discovery rate, see Supplementary Table 3 for corrected values.

Dichotomising end-of-study MMSE led to a similar ordering of the HR of different exposures on cognitive impairments (Supplementary Figure 1, Supplementary Figure 2) to the use of MMSE as a continuous outcome.

There were no interactions with age or sex in the relationship between cognitive performance (MMSE) and variability in any of the measurements (supplementary Table 4). In older people compared with younger people, the aHR was smaller for CVD with greater blood pressure variability ($p_{interaction}<0.01$) and increasing heart rate variability ($p_{interaction}=0.01$) (supplementary Tables 5 and 6). There were no interactions between sex and variability in any of our measurements on the aHR for CVD, nor any other interactions between age and variability (supplementary Table 4).

4. Discussion

Higher visit-to-visit variability in BP, HR, FPG, cholesterol and weight were associated with poorer cognitive performance and a higher risk of cardiovascular disease (CVD) after accounting for mean levels. The effect of visit-to-visit variability was similar across biological measurements. A one-point increase in z-score of variability (SD) of a measurement was associated with an ~0.1 point lower MMSE, and between a 10 % to 20 % higher incidence of CVD. People with more measurements with high visit-to-visit variability had a higher risk of CVD and worse cognitive performance.

Similar to our findings, several studies have previously found that higher visit-to-visit variability in biological measurements are associated with poorer cognition[2,4,7,30] and greater risk of CVD.[3,8,16,17] Prior evidence suggests that high visit-to-visit variability in multiple measurements is associated with poorer outcomes in a step wise manner, for both cognitive[14,15] and CVD[8,16,17] related outcomes. Our study, which uses data from 40 countries, strengthens the generalisability of these findings. Further, our study strengthens the quality of evidence by using data from a RCT, which provides many advantages such as strict protocols for collecting the measurements of interest, trained administrators across sites, and recording of baseline

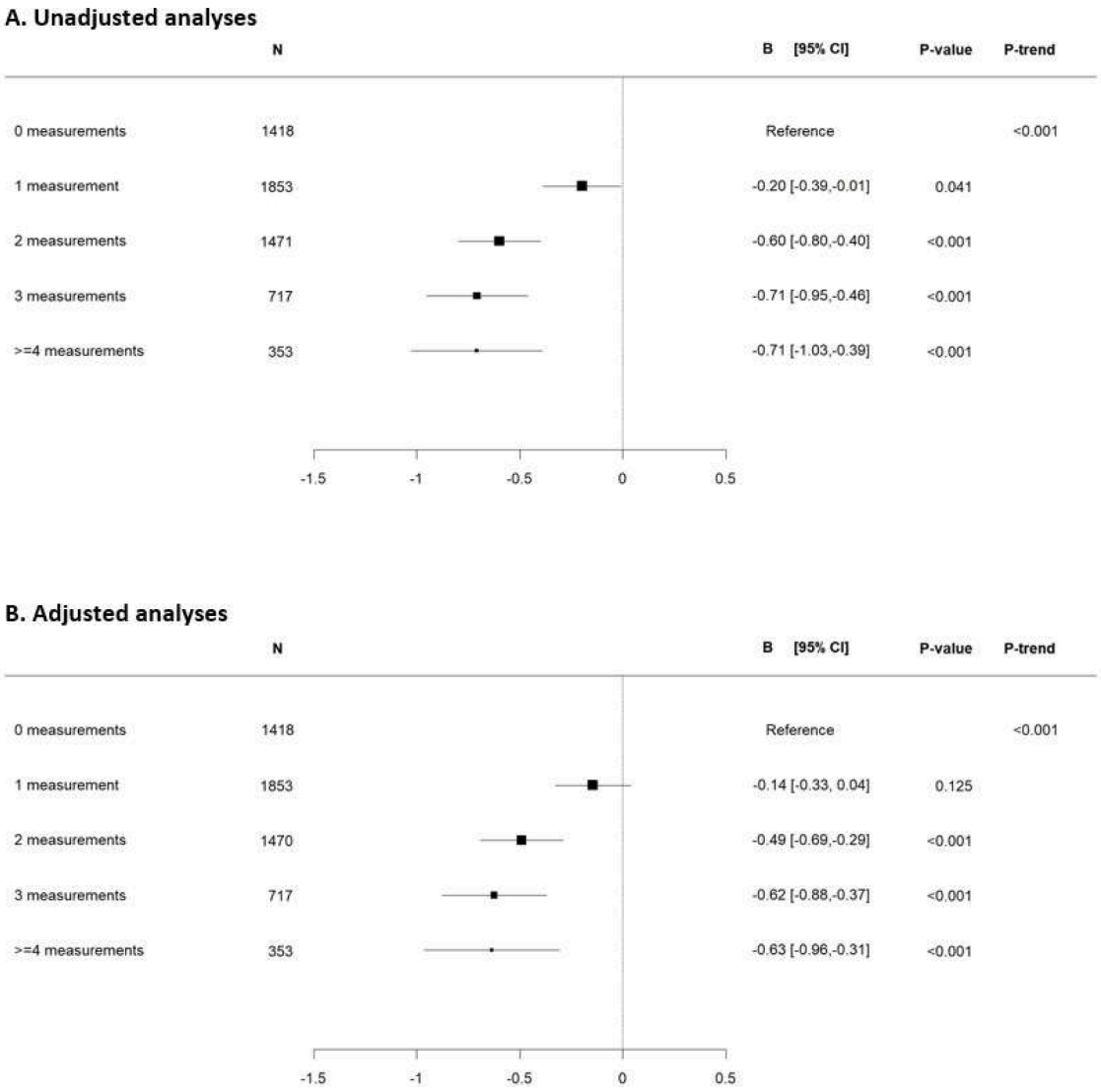

Fig. 3. MMSE mean difference between participants with 0 high variability measurements and those with 1, 2, 3 or 4 or more measurements with high variability, showing A. adjusted for baseline MMSE only and B. adjusted for baseline MMSE, age, sex, education, BMI, smoking status, treatment allocation, hypertension, diabetes, prior stroke, prior MI, mean measurement values, and time..
Abbreviations: MMSE: mini-mental state examination, B: beta, CI: confidence interval. All significant p-values survived correction for false discovery rate, see Supplementary Table 3 for corrected values.

characteristics, prior health, and adjudicated adverse events. Further strengths of this study include the large sample size and completeness of data.

Our study had some limitations. First, approximately 14 % of participants had died by end of trial which limited end-of-trial measurement of cognitive impairment, however we accounted for the competing risk of non-CV death in our CVD analyses. Second, final cognitive assessment was not completed in around 5 % of survivors, although this is low loss to follow-up compared to other longitudinal studies with cognitive data.[31,32] Third, participants were not representative of those in the wider population, specifically, participants consented to trial participation, were mostly male, were dysglycemic, and had a high prevalence of cardiovascular disease and risk. Fourth, we excluded participants who had fewer than 3 time points per measurement, and in our analyses of the additive effects of multiple measurements, we excluded participants who did not have a measure of variability for all 6 measures, which may have introduced further bias, however baseline characteristics were similar in both groups. Fifth, follow-up was relatively short for a study involving cognitive outcomes (median 6 years). Sixth, in certain cases, when accounting for covariates in the adjusted analyses, the effect size of the estimate increased rather than attenuated, contrary to expectation. This suggests the adjusted analyses may be susceptible to collider bias.[33] Seventh, we solely used standard deviation (SD) as the measure of visit-to-visit variability. We used SD for ease of calculation and interpretation as it is a commonly used measure, however standard deviation can be affected by extreme values which measures such as the coefficient of variation are less sensitive to. However, evidence suggests that results are minimally affected by the choice of method used to measure variability.[8,14,15] Finally, measurements collected were sometimes the target of intervention (i.e., FPG). However, we only took measurements at least 3 months post-randomisation to account for changes in FPG due to the introduction of the trial drug.

Although our results may be explained by variability causing both cognitive impairments and CVD (for example though effects on the vasculature), they are also consistent with other explanations. Reverse causality is possible, although the very small effect of excluding participants with CVD events during trial makes this less likely. A cause proximal to variability is possible. Our results support this explanation. First, the effect of visit-to-visit variability in different measurements was

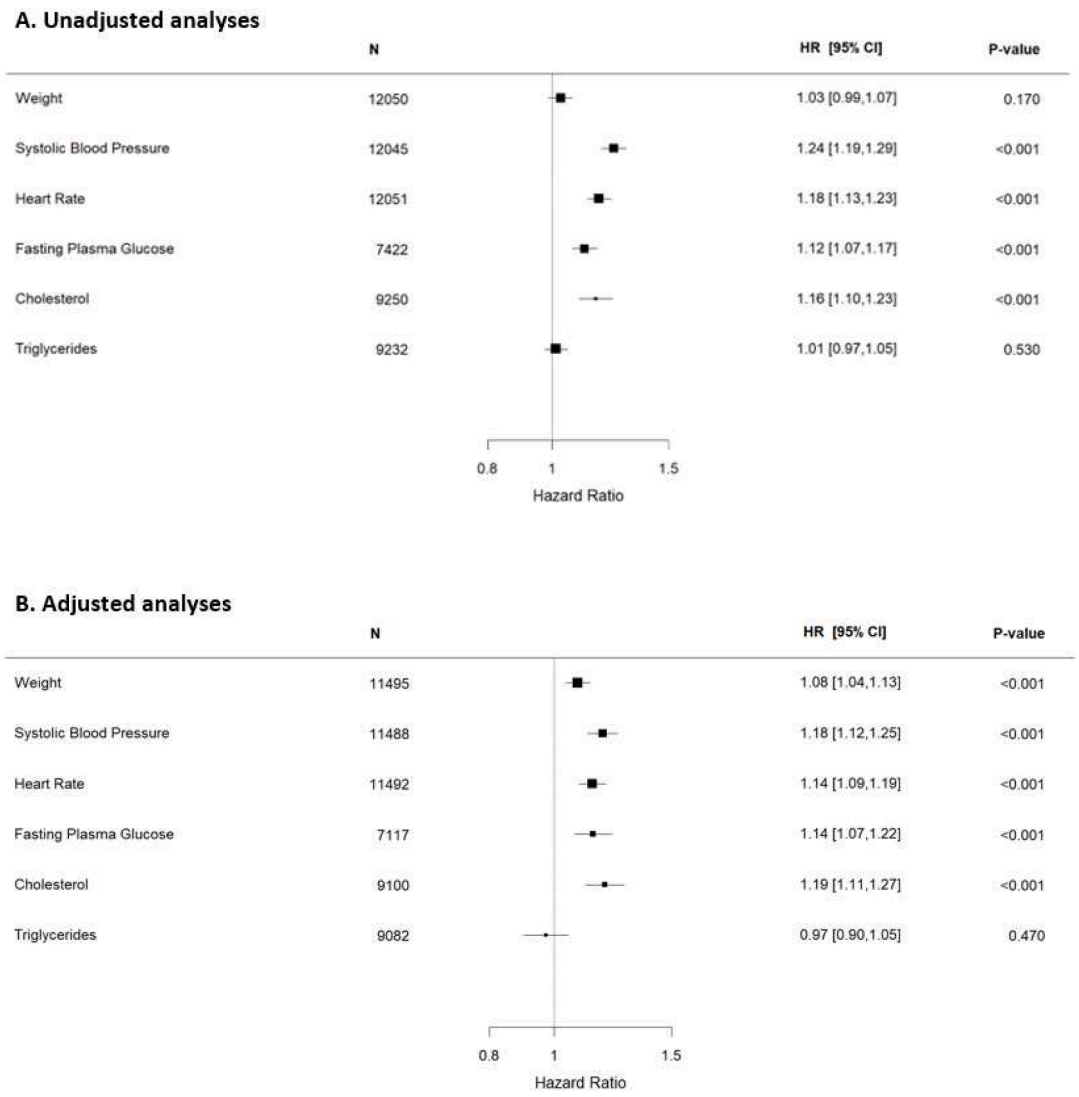

Fig. 4. Hazard ratio of CVDˆ per one unit increase in visit-to-visit variability, showing A. unadjusted, and B adjusted for baseline MMSE, age, sex, education, BMI, smoking status, treatment allocation, hypertension, diabetes, prior stroke, prior MI, and mean measurement values. Where variability is measured as the z-score of the SD (i.e., how many standard deviations above or below the mean SD each participant's value lies) for each measurement.
ˆ CVD defined as non-fatal stroke, non-fatal myocardial infarction (MI), or death from cardiovascular causes. Abbreviations: CVD: cardiovascular disease, N: number, HR: hazard ratio, CI: confidence interval. All significant p-values survived correction for false discovery rate, see Supplementary Table 3 for corrected values.

similar, which if causal would suggest a similar mechanism across many biological measurements. Second, there was an effect of visit-to-visit variability on both CVD and cognitive impairment which would need different causal pathways, this is further supported by the association between variability and other outcomes (for example non-vascular death[34]). The likeliest explanation is that the observed visit-to-visit variability in biological measurements is associated with frailty (and loss of homeostasis), which leads to vulnerability to many conditions of ageing (including cognitive impairment and CVD).[19–21]

There are currently no indications for measuring visit-to-visit variability of one or more measures, either for disease prediction or planning treatment.[18,35] The effect sizes are relatively small and may not confer much benefit above monitoring mean values, and there is no established threshold for 'normal' variability. Measurement of visit-to-visit variability e.g., which measurements should be collected, how often, for how long, and what measure of variability would be most appropriate, are still open questions.

There is a need to establish whether there is a causal relationship between visit-to-visit variability and poorer cardiovascular and cognitive outcomes, or whether this is instead a marker of increased risk (for example a marker of frailty).[36] Ideally, randomised trials to test the effect of visit-to-visit variability on such outcomes would be conducted, however these trials may not be possible as there are currently no therapies or mechanisms known to control variability without affecting the mean measurement values. [35,36]

5. Conclusions

This study examined the relationship between visit-to-visit variability in markers of cardiovascular risk with cognitive performance and risk of CVD, finding that higher levels of visit-to-visit variability in BP, HR, FPG, weight, and cholesterol are associated with poorer outcomes. We further found that the effects of high visit-to-visit variability were additive, whereby participants with greater numbers of high-variability measurements experienced worse outcomes. The clinical implications of these results, however, remain unclear.

CRediT authorship contribution statement

Laura Sherlock: Conceptualization, Formal analysis, Methodology,

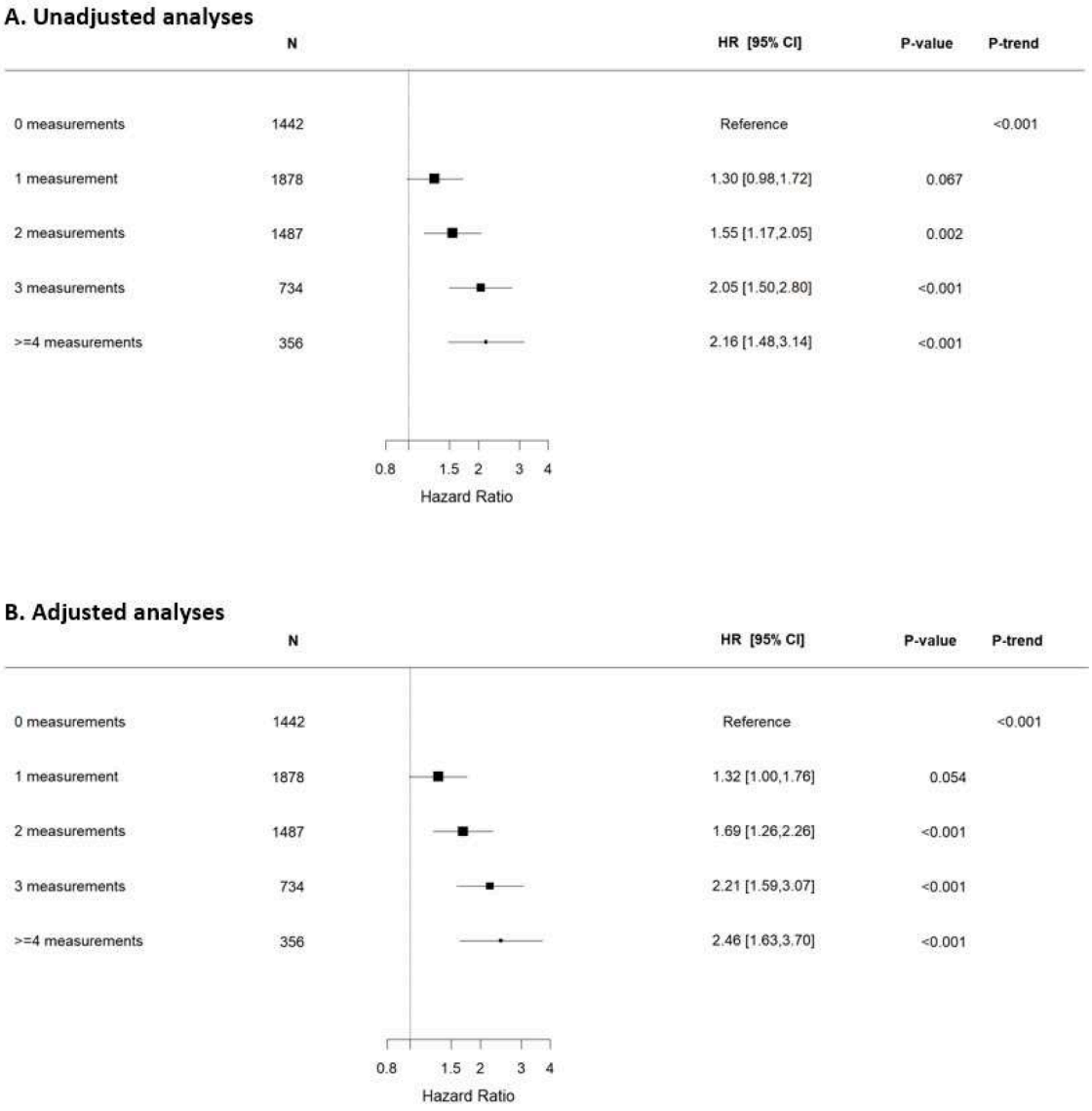

Fig. 5. Hazard ratio of CVDˆ in participants with 1, 2, 3 or 4 or more high variability measurements versus those with 0, showing A. unadjusted and B. adjusted for baseline MMSE, age, sex, education, BMI, smoking status, treatment allocation, hypertension, diabetes, prior stroke, prior MI, and mean measurement values.
ˆ CVD defined as non-fatal stroke, non-fatal myocardial infarction (MI), or death from cardiovascular causes. Abbreviations: CVD: cardiovascular disease, N: number, HR: hazard ratio, CI: confidence interval. All significant p-values survived correction for false discovery rate, see Supplementary Table 3 for corrected values.

Table 4
Coefficients of Pearson's correlations between visit-to-visit variability in measurements.

	Weight	Systolic Blood Pressure	Heart Rate	Fasting Plasma Glucose	Triglycerides
Systolic Blood Pressure	0.088**				
Heart Rate	0.098**	0.196**			
Fasting plasma Glucose	0.099**	0.085**	0.105**		
Triglycerides	0.026	0.007*	0.019	0.091**	
Cholesterol	0.039**	0.068**	0.065**	0.067**	0.232**

* $p < 0.01$.
** $p < 0.001$.

Visualization, Writing – original draft, Writing – review & editing. **Shun Fu Lee:** Conceptualization, Methodology, Writing – review & editing. **Tali Cukierman-Yaffe:** Conceptualization, Methodology, Writing – review & editing. **Darryl Leong:** Conceptualization, Methodology, Writing – review & editing. **Hertzel C. Gerstein:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Jackie Bosch:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Graciela Muniz-Terrera:** Conceptualization, Methodology, Supervision. **William N. Whiteley:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

TCY has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Eli Lilly, Sanofi, MSD, Novo Nordisk, Medtronic, Geffen Medical, AstraZeneca, and Boehringer Ingelheim. HCG has done consultancy work for Abbott, AstraZeneca, Eli Lilly and Company, Novo Nordisk, Sanofi,

Kowa, Pfizer and Hanmi; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Eli Lilly and Company, Jiangsu-Hanen, Carbon Brand, Novo Nordisk, Sanofi and Boehringer Ingelheim. WNW has done consultancy work for Bayer; data/safety monitoring for the Universities of Calgary, Manchester, Oxford and Utrecht; has received compensation from UK Courts for expert witness services; and compensation from American Heart Association for other services. All other authors report no competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2024.100223.

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