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## **Relations of demographic and clinical factors with cardiovascular autonomic function in a population-based study: an assessment by quantile regression**

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**Running title:** Quantile regression of CV autonomic function

## Abstract

**Background:** The relationships of many factors with cardiovascular autonomic function (CVAF) outcome parameters may not be uniform across the entire distribution of the outcome. We examined how demographic and clinical factors varied with different subgroups of CVAF parameters.

**Methods:** Quantile regression was applied to a cross-sectional analysis of 4,167 adults (56% male; age range, 50-84 years) from 4 ethnic groups (3,419 New Zealand European, 303 Pacific, 227 Maori and 218 South Asian) and without diagnosed cardiac arrhythmia. Pulse rate variability (root mean square of successive differences (RMSSD) and standard deviation of pulse intervals) and baroreflex sensitivity were response variables. Independent variables were age, sex, ethnicity, brachial and aortic blood pressure (BP) variables, BMI and diabetes.

**Results:** Ordinary linear regression showed that age, sex, Pacific and Maori ethnicity, BP variables, BMI and diabetes were associated with CVAF parameters. But quantile regression revealed that, across CVAF percentiles, the slopes for these relationships: 1) varied by more than 10-fold in several cases and sometimes changed direction and, 2) noticeably differed in magnitude often (by >3-fold in several cases) compared to ordinary linear regression coefficients. For instance, age was inversely associated with RMSSD at the 10<sup>th</sup> percentile of this parameter ( $\beta=-0.12$  ms/year, 95% confidence interval=-0.18 to -0.09 ms/year) but had a positive relationship at the 90<sup>th</sup> percentile ( $\beta=3.17$  ms/year, 95% confidence interval=2.50 to 4.04 ms/year).

**Conclusions:** The relationships of demographic and clinical factors with CVAF parameters are, in many cases, not uniform. Quantile regression provides an improved assessment of these associations.

**Keywords:** Autonomic nervous system, heart rate variability, blood pressure, pulse waveform, body mass index, diabetes mellitus, ethnic groups

## Introduction

Cardiovascular autonomic function (CVAF) is an important aspect of cardiovascular health. Variables reflecting this, such as heart rate variability (HRV) and baroreflex sensitivity (BRS), predict risk of cardiovascular events.<sup>1-3</sup> Impaired autonomic function has been identified as a factor in the pathogenesis of hypertension. In support of this, both parasympathetic and sympathetic activity have physiological effects on blood pressure (BP)<sup>4</sup> and low HRV is associated with greater risk of incident hypertension.<sup>5</sup> Further, impaired HRV predicts new-onset atrial fibrillation,<sup>6</sup> which is associated with an increased risk of cardiovascular morbidity and mortality.<sup>7,8</sup> Identifying determinants of CVAF is thus useful for understanding how factors may impact on cardiovascular health.

Factors that may influence CVAF are age, sex, ethnicity, BP, body mass index (BMI) and diabetes;<sup>9-12</sup> all are well-known cardiovascular risk factors. However, analyses in past studies of CVAF were carried out using ordinary linear regression, which models only the mean of this outcome. Important relationships may be missed because cardiovascular disease/events correlate positively with HRV parameters at high levels of these measures<sup>3,13,14</sup> but inversely at lower levels.<sup>1,3,5</sup> Thus, the relationship between CVAF and cardiovascular events is not uniform across the entire distribution of the former. Further, HRV measures frequently have skewed distributions,<sup>10</sup> suggesting that determinants of these parameters may affect specific regions (percentiles) of these distributions more than others. For example, a positively skewed distribution might arise, in part, from a factor particularly affecting HRV values at the upper end of the distribution. In view of this, a more comprehensive and useful evaluation of associations between various factors and HRV measures would be attained by carrying out subgroup analyses in different regions of the HRV distribution.

Another gap in prior research is knowledge of whether CVAF varies with Polynesian and South Asian ethnicities. This is significant as these ethnic groups have a higher prevalence of cardiovascular disease relative to European (white) populations.<sup>15,16</sup> Further, previous studies have evaluated relationships of CVAF with brachial BP but not with other arterially-related parameters. These include augmentation index, peak reservoir pressure and excess pressure integral; parameters which may predict cardiovascular burden independently of brachial BP.<sup>17-19</sup>

We sought to examine how CVAF parameters vary with demographic and clinical factors. To build on past research, these associations were evaluated across various percentiles of the distribution of these CVAF measures, we included participants of Polynesian (Maori and Pacific) and South Asian ethnicity, and measurements taken from the aortic pressure waveform were included in analyses.

## **Methods**

### *Participants*

The present study is an analysis of baseline data collected in the ViDA (Vitamin D Assessment) study, a randomised controlled trial of the health effects of vitamin D supplementation. Inclusion criteria were men and women aged 50-84 years and resident in Auckland at recruitment. Exclusion criteria included: 1) diagnosis of a terminal illness and/or in hospice care, 2) intending to leave New Zealand during the follow-up period, 3) taking vitamin D supplements (including cod liver oil) of >600 IU per day, 4) history of renal stones, hypercalcaemia, or medical conditions that can cause hypercalcaemia and 5) baseline serum calcium >2.50 mmol/L. All baseline data were collected between 2011 and 2012. Ethics approval was provided by the Ministry of Health Multi-region Ethics committee. Written,

informed consent was obtained from each participant. Full details of the study design have been published elsewhere.<sup>20</sup>

#### *Demographic and non-BP, clinical variables*

All measurements were carried out by trained staff using a standardised protocol. Questionnaires administered by interviewers were used to collect data on age, sex, ethnicity (defined by self-identification) and history of diabetes. Past diagnosis of a cardiac arrhythmia was also determined from these questionnaires and from Ministry of Health hospitalisation data; since HRV assessment is traditionally applied to people without a cardiac arrhythmia. Without shoes and in light clothing, height ( $\pm 0.1$  cm) was measured with a stadiometer and weight ( $\pm 0.1$  kg) with digital scales. Body mass index (BMI) was calculated as weight (kg)/height (m)<sup>2</sup>.

To adjust for the effect of antihypertensive medications on the CVAF parameters, prescriptions dispensed for days of supply that encompassed the interview date were recorded from Ministry of Health data. Antihypertensive medicines were categorised into beta-blockers and non-beta-blockers since these drug classes may differentially affect CVAF parameters.<sup>21,22</sup>

#### *BP variables*

After 15 minutes resting and while sitting, brachial BP ( $\pm 1$  mmHg) was measured three times with an Omron T9P oscillometric device (Omron Healthcare, Kyoto, Japan) above the cubital fossa of the left arm and the mean of the two closest measurements was used for analyses. Suprasystolic oscillometry was carried out using a BP+ device (Uscom, Sydney, Australia) (formerly known as a R6.5 cardiovascular monitor; Pulsecor, Auckland, New Zealand), with an appropriately-sized cuff positioned over the left upper arm. The BP+ device has been

shown to: 1) yield central systolic blood pressures that are highly correlated with those assessed by catheter measurement at the ascending aorta or aortic arch<sup>23</sup> and, 2) measure central systolic BP with good intratest and intertest reliability.<sup>24</sup> To improve the quality of the waveforms used in analyses, we decided *a priori* to exclude readings with a signal-to-noise ratio of <6 dB.

Augmentation index (AIx), a predictor of CV events,<sup>17</sup> was calculated from the aortic pressure waveform using custom-written Matlab software (Mathworks, Natick, MA). Aortic pressure was separated into reservoir and wave components using custom-written Matlab software. Reservoir pressure was calculated from pressure measurements only, as described elsewhere.<sup>18</sup> Peak reservoir pressure was calculated as the amplitude of the reservoir pressure waveform, which has been found to associate positively with the risk of cardiovascular events independently of brachial BP.<sup>19</sup> Excess pressure was calculated as measured aortic pressure minus reservoir pressure.<sup>19</sup> The integral of the excess pressure waveforms (area under these waveforms) over the cardiac cycle was used to calculate excess pressure integral (EPI). EPI measures pressure associated with excess ventricular work and has been shown to predict CV events independently of brachial SBP.<sup>18</sup>

#### *CVAF measures*

Pulse rate variability was assessed from the variability of the beat duration of the aortic pressure waveforms derived from the BP+ device. The waveforms spanned approximately 10 seconds; thus analysis was performed on approximately 10 to 12 pulse intervals, a period adequate for valid measurement of HRV.<sup>25-29</sup> Two time-domain measures were used: root mean square of successive differences (RMSSD) and standard deviation (SD) of pulse intervals (in ms; analogous to SD of NN intervals of an electrocardiographic record).<sup>30</sup>

RMSSD (in ms) was calculated as the square root of the mean of the squared differences of the duration of successive pulse intervals and reflects parasympathetic activity.<sup>30</sup>

BRS was assessed using the sequence method, which establishes the slope of the relationship between changes in pulse interval and SBP across successive cardiac cycles.<sup>31,32</sup> Pulse intervals were paired with the SBP (maximum amplitude of the pressure waveform) of the preceding cardiac cycle (that is, a one-beat delay), as described elsewhere.<sup>31,32</sup> Instances in which SBP and pulse intervals (PI) both increased (+PI/+SBP) or decreased (-PI/-SBP) from one beat to the next were detected. Due to the limited number of beats, we did not enforce the practice<sup>31</sup> that these changes had to occur over at least three consecutive beats. The minimum SBP change between pulse intervals that was accepted was 1 mmHg. BRS (in ms/mmHg) was calculated as the mean of all +PI/+SBP and -PI/-SBP slopes.

### *Statistical analysis*

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Because of the influence of cardiac arrhythmias on pulse rate variability, analyses were restricted to participants without previously diagnosed cardiac arrhythmia. In a subgroup analysis of this sample, we performed a supplementary set of analyses excluding people with an RMSSD of >100 ms as these values may be indicative of unknown cases of atrial fibrillation.<sup>33</sup> Factors that were associated with CVAF variables were identified by multiple ordinary linear regression and quantile regression. The latter is a statistical approach that examines predictors of different percentiles of a response variable. While ordinary linear regression models only the mean of a dependent variable, quantile regression can model any part of the distribution of it, thus giving more comprehensive results.<sup>34</sup> For this technique, we assessed relationships in 19 percentile groups (5 percentiles apart) ranging from the 5<sup>th</sup> to the 95<sup>th</sup> percentile (that is, the 5<sup>th</sup>, 10<sup>th</sup>, 15<sup>th</sup>, ..., 90<sup>th</sup> and 95<sup>th</sup> percentiles). **Linearity of these associations was checked in**



each percentile group of the response (CVAF) variable. To evaluate whether the regression coefficients varied across the quantiles, we used the *qinteract* option in PROC QUANTREG. We compared quantile regression results with those from ordinary linear regression; this approach has been applied in other studies that utilise quantile regression<sup>34</sup> and allows a comparison with other HRV studies that use ordinary linear regression. These multivariable relationships were adjusted for age, sex, ethnicity and use of antihypertensive medicines (none, non-beta-blockers or beta-blockers). A two-tailed  $P < 0.05$  was considered statistically significant.

## Results

Table 1 shows the characteristics of the participants, which comprised 4,167 people. Figures 1-3 show differences in CVAF measures (Figure 1 for RMSSD, Figure 2 for SD pulse intervals and Figure 3 for BRS) per unit difference (or across groups for categorical variables) in demographic/clinical factors by percentile of the CVAF measure. Table 2 lists these effect sizes for selected percentiles (10<sup>th</sup> and 90<sup>th</sup>) and tabulates effect sizes estimated by ordinary linear regression. Age was inversely related to both RMSSD up to the 60<sup>th</sup> percentile of this parameter and SD of pulse intervals up to the 45<sup>th</sup> percentile. But at higher percentiles, the age coefficients markedly increased, becoming positive (both  $P < 0.0001$  for trend). Compared to females, males had lower RMSSD and SD of pulse intervals at low-middle percentiles ( $\leq 60^{\text{th}}$ ) of these parameters but higher levels at high percentiles ( $P = 0.0006$  and  $0.03$ , respectively). Relative to Europeans, Pacific people had higher RMSSD at upper percentiles of this parameter and lower SD of pulse intervals at low percentiles. Maori ethnicity was associated with higher RMSSD and SD of pulse intervals at high percentiles especially. South Asian ethnicity was unrelated to the three CVAF parameters. Brachial SBP, brachial DBP and peak reservoir BP had inverse relationships with BRS that were greater at higher percentiles, with

the maximum quantile-specific slope increase being nearly 10-fold in each case ( $P < 0.0001$ ,  $P = 0.001$  and  $P = 0.002$ , respectively, for trends). AIx was positively associated with all three CVAF variables (at most or all quantiles) but especially so at higher quantiles (all  $P < 0.0001$ ); the greatest increase in coefficients was about 11, 12 and 10 times for RMSSD, SD of pulse intervals and BRS, respectively. Excess pressure integral was positively associated with BRS between the 75<sup>th</sup> and 85<sup>th</sup> percentiles only ( $P = 0.01$  for trend across all quantiles). BMI was unrelated to SD of pulse intervals at low levels of this CVAF parameter but had increasingly positive associations at higher percentiles. Conversely, BMI had increasingly inverse relationships with BRS at higher percentiles of this CVAF measure (maximum slope difference = 13-fold;  $P = 0.004$ ). Diabetes was associated with a lower RMSSD up to the 65<sup>th</sup> percentile of the latter and SD of pulse intervals up to the 30<sup>th</sup> percentile. Compared to percentile-specific coefficients determined from quantile regression (Figures 1-3), regression coefficients estimated by ordinary linear regression (Table 2) noticeably differed in magnitude often (by  $>3$  times in several cases) and differed in direction sometimes.

In a subgroup analysis of this sample, we excluded people ( $n = 385$ ) with an RMSSD of  $>100$  ms, which may be indicative of unknown cases of atrial fibrillation, and repeated the ordinary linear and quantile regression analyses (Supplementary Table S1, Supplementary Figures S1-S3). As shown in these results, for RMSSD and SD of pulse intervals, the slopes at high percentiles of these parameters generally deviated less from those at lower percentiles. Age was still inversely related to RMSSD at lower percentiles of this parameter but now even more so at higher quantiles ( $P = 0.002$ ), with the greatest slope increase being by a factor of nearly 3. Male sex was still associated with lower RMSSD and SD of pulse intervals at low quantiles but now increasingly so (up to 6- and 11-fold slope differences, respectively) at higher quantiles ( $P = 0.005$  and  $0.02$ , respectively, for overall trends). For BRS, the quantile-

plot trends were similar in the subgroup analysis sample (Supplementary Figures S1-S3) compared to in the total sample (Figures 1-3).

## Discussion

This study showed that, among people without cardiac arrhythmias, age, sex, Pacific and Maori ethnicity, BP variables, BMI and diabetes were associated with CVAF parameters. But, in many cases, these associations varied along the distributions of CVAF measures, becoming stronger at higher percentiles and sometimes changing direction.

In several cases, slopes for each percentile were noticeably different from those obtained from ordinary linear regression. For instance, we reported that, across percentiles, slopes increased by up to more than 10-fold and even changed direction in some cases (Table 2 and horizontal lines in Figures 1-3). This indicates that, rather than reliance on ordinary linear regression, quantile regression provides a more comprehensive assessment of factors associated with CVAF.

Ordinary linear regression relies on meeting assumptions of linearity of associations and both homoscedasticity and normality of regression residuals. Because our observed relationships differed by levels of the HRV outcome, ordinary linear regression would be invalid or inadequate by violating these assumptions. The importance of this problem to HRV studies is increased by the finding that these assumptions are often not tested prior to presenting results of linear regression.<sup>35</sup> In contrast, quantile regression does not need assumptions about the distribution of the residuals and is not influenced by outliers or skewness in the distribution of the response variable.<sup>36-38</sup> Thus, in addition to being more informative than ordinary linear regression for studying HRV, quantile regression is a more adequate or valid statistical method.

At low percentiles of RMSSD and SD pulse intervals, these response variables were inversely associated with age (which concurs with previous HRV studies<sup>10</sup>) and were lower in males. However, these relationships were positive at higher percentiles (Table 2, Figures 1-2). Given that cardiovascular disease/events correlate positively with HRV parameters at high levels of these measures<sup>3,13</sup> but inversely at lower levels,<sup>1,3,5</sup> this suggests that these age- and sex- related variations in pulse rate variability parameters may contribute to the increased risk of cardiovascular disease observed among older people and males.

Polynesian and South Asian people experience greater cardiovascular disease morbidity compared to white populations.<sup>15,16</sup> Given that CVAF measures predict cardiovascular events,<sup>1-3</sup> ethnic differences in these parameters might contribute to this discrepancy in cardiovascular disease burden. However, there is a lack of knowledge about whether these measures vary between these ethnic groups. In this study, these parameters did not vary between South Asian and European groups, suggesting that they might not mediate differences in cardiovascular burden between these populations. In contrast, relative to Europeans, Maori people had higher RMSSD and SD of pulse intervals at high percentiles of these parameters, while Pacific people had higher RMSSD at high percentiles and lower SD of pulse intervals at low percentiles (Table 2, Figures 1-2). Thus, these differences could contribute to the higher cardiovascular disease burden observed in Polynesian populations.

Age and BMI both associate inversely with BRS.<sup>11</sup> The present study extends this prior research by showing that the sizes of these relationships vary across the BRS distribution (Figure 3). In addition, while previous studies have shown that BRS decreases with brachial SBP,<sup>11</sup> which is supported by the present study, our findings also show that its relationships with brachial SBP, brachial DBP and peak reservoir BP are increasingly inverse at higher BRS percentiles (Figure 3). We further add to this past work by demonstrating that

AIx is positively related to BRS at high percentiles of the latter but not at low percentiles (Figure 3).

As for limitations of this study, the observational design (cross-sectional) precludes causal inferences. The CVAF measures were collected over typically 10-12 seconds and, while several studies demonstrate that time-domain measures (especially RMSSD) calculated from 10-second recordings reliably estimate HRV, a longer sampling interval (typically 5-minute) is preferable.<sup>25-29</sup> Nevertheless, our results are consistent with those of previous studies that investigated correlates of parameters from  $\geq 5$ -minute HRV recordings, which supports the validity of our HRV measures. For instance, in line with prior research, our results (Table 2, Figures 1 and 3) showed that, at most percentiles, RMSSD decreased with age<sup>10</sup> and was lower among diabetics,<sup>12</sup> while BRS decreased with age, brachial BP and BMI.<sup>11</sup>

In summary, we observed that age, sex, Pacific and Maori ethnicity, BP variables, BMI and diabetes were related to CVAF measures but these associations varied across CVAF percentiles. The quantile-dependency of these relationships could account, at least in part, for the skewed distributions observed with CVAF measures. In addition, they highlight the importance of quantile regression in examining these associations and that prior studies which relied on ordinary linear regression are likely to have not captured these variations by percentile.

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**Disclosure**

Andrew Lowe is a shareholder in and has consulted for Uscom Limited.

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## Figure captions

- Figure 1** Point estimates and 95% confidence intervals (shaded areas) for differences in root mean square of success differences (RMSSD) per unit difference in demographic/clinical factors (adjusted for age, sex ethnicity and antihypertensive use). The horizontal line represents the point estimate derived from ordinary linear regression. EPI = Excess pressure integral. The RMSSD values (ms) at each of the 19 percentiles (x-axis coordinates) are 8.5 (5<sup>th</sup> percentile), 10.5, 12.2, 13.8, 15.1, 16.6, 18.0, 19.4, 21.0, 22.7 (median), 24.7, 26.9, 29.4, 32.7, 37.1, 43.4, 54.8, 87.4 and 213.1 (95<sup>th</sup> percentile)
- Figure 2** Point estimates and 95% confidence intervals (shaded areas) for differences in standard deviation of pulse intervals (SDPI) per unit difference in demographic/clinical factors (adjusted for age, sex ethnicity and antihypertensive use). The horizontal line represents the point estimate derived from ordinary linear regression. EPI = Excess pressure integral. The SDPI values (ms) at each of the 19 percentiles (x-axis coordinates) are 4.3 (5<sup>th</sup> percentile), 5.3, 6.2, 6.9, 7.7, 8.6, 9.5, 10.5, 11.6, 12.9 (median), 14.6, 16.7, 18.8, 22.2, 26.0, 30.2, 38.2, 55.1 and 98.6 (95<sup>th</sup> percentile)
- Figure 3** Point estimates and 95% confidence intervals (shaded areas) for differences in baroreflex sensitivity (BRS) per unit difference in demographic/clinical factors (adjusted for age, sex ethnicity and antihypertensive use). The horizontal line represents the point estimate derived from ordinary linear regression. EPI = Excess pressure integral. The BRS values (ms/mmHg) at each of the 19 percentiles (x-axis coordinates) are 0.93 (5<sup>th</sup> percentile), 1.35, 1.72, 2.03, 2.38, 2.71, 3.02, 3.40, 3.84, 4.23 (median), 4.67, 5.27, 5.79, 6.48, 7.54, 8.79, 10.09, 12.65 and 17.59 (95<sup>th</sup> percentile)

**Table 1.** Characteristics of participants

| Variable                                |                       | N (%) or mean $\pm$ standard deviation* |
|---|-----------------------|---|
| Age (years)                             |                       | 65.9 $\pm$ 8.2                          |
| Male                                    | Male                  | 2,348 (56)                              |
|   | Female                | 1,819 (44)                              |
| Ethnicity                               | European              | 3,419 (82)                              |
|   | Maori                 | 227 (5)                                 |
|   | Pacific               | 303 (7)                                 |
|   | South Asian           | 218 (5)                                 |
| Brachial SBP (mmHg)                     |                       | 139.2 $\pm$ 18.7                        |
| Brachial DBP (mmHg)                     |                       | 78.2 $\pm$ 10.2                         |
| Augmentation index (%)                  |                       | 28.7 $\pm$ 12.2                         |
| Excess pressure integral (mmHg.s)       |                       | 3.89 $\pm$ 1.80                         |
| Peak reservoir BP (mmHg)                |                       | 122.0 $\pm$ 16.4                        |
| Pulse rate (beats/minute)               |                       | 63.3 $\pm$ 10.0                         |
| BMI (kg/m <sup>2</sup> )                |                       | 28.4 $\pm$ 5.1                          |
| Diabetes (n (%))                        | Yes                   | 490 (12)                                |
|   | No                    | 3,677 (88)                              |
| Antihypertensive use (n (%))            | None                  | 2,664 (64)                              |
|   | Non- $\beta$ -blocker | 1,079 (26)                              |
|   | $\beta$ -blocker      | 424 (10)                                |
| RMSSD (ms), median $\pm$ IQR            |                       | 22.7 $\pm$ 22.0                         |
| SD of pulse intervals, median $\pm$ IQR |                       | 12.9 $\pm$ 18.3                         |
| BRS (ms/mmHg), median $\pm$ IQR         |                       | 4.2 $\pm$ 5.2                           |

Abbreviations: BMI, body mass index; BP, blood pressure; BRS, baroreflex sensitivity; DBP, diastolic BP; IQR, interquartile range; RMSSD, root mean square of successive differences; SBP, systolic BP; SD, standard deviation. \*Unless otherwise indicated.

**Table 2.** Regression coefficients of cardiovascular autonomic function predictors estimated by ordinary linear regression or quantile regression

| Outcome  | Independent variable |                          | Regression coefficient (95% confidence interval) |                             |                              |
|--|----------------------|--------------------------|--|-----------------------------|------------------------------|
|  |                      |                          | OLR  | 10 <sup>th</sup> percentile | 90 <sup>th</sup> percentile  |
| RMSSD<br>(ms)  | Age (years)          |                          | <b>1.12 (0.72, 1.53)</b>                         | <b>-0.12 (-0.18, -0.09)</b> | <b>3.17 (2.50, 4.04)</b>     |
|  | Sex <sup>†</sup>     | Male                     | <b>10.15 (3.94, 16.37)</b>                       | <b>-1.32 (-1.97, -0.49)</b> | <b>17.19 (3.65, 37.30)</b>   |
|  |                      | Ethnicity <sup>†</sup>   |  |                             |                              |
|  |                      | Pacific                  | 8.67 (-3.43, 20.80)                              | -0.61 (-2.39, 0.17)         | <b>16.87 (4.04, 45.42)</b>   |
|  |                      | Maori                    | <b>19.04 (5.27, 32.81)</b>                       | 0.58 (-1.36, 1.76)          | <b>57.89 (16.32, 136.08)</b> |
|  |                      | South Asian              | -7.56 (-21.64, 6.53)                             | 0.14 (-0.79, 1.82)          | -5.57 (-21.62, 28.02)        |
|  |                      | Brachial SBP (mmHg)      | -0.08 (-0.24, 0.09)                              | -0.01 (-0.03, 0.01)         | -0.15 (-0.43, 0.27)          |
|  |                      | Brachial DBP (mmHg)      | -0.18 (-0.13, 0.48)                              | -0.01 (-0.06, 0.01)         | 0.11 (-0.51, 0.67)           |
|  |                      | Augmentation index (%)   | <b>0.40 (0.12, 0.68)</b>                         | <b>0.15 (0.13, 0.19)</b>    | <b>1.12 (0.21, 1.69)</b>     |
|  |                      | EPI (mmHg.s)             | -0.53 (-2.35, 1.29)                              | <b>0.59 (0.33, 0.79)</b>    | 0.13 (-2.08, 5.12)           |
|  |                      | Peak reservoir BP (mmHg) | -0.06 (-0.25, 0.13)                              | 0.02 (-0.00, 0.03)          | -0.14 (-0.48, 0.27)          |
|  |                      | BMI (kg/m <sup>2</sup> ) | -0.40 (-0.26, 1.06)                              | -0.06 (-0.11, 0.00)         | 0.49 (-0.37, 2.40)           |
|  |                      | Diabetes                 | -4.53 (-14.58, 5.52)                             | <b>-1.70 (-2.67, -1.03)</b> | -4.58 (-42.47, 45.95)        |
| Standard<br>deviation of<br>pulse<br>intervals<br>(ms) | Age (years)          |                          | <b>0.39 (0.24, 0.53)</b>                         | <b>-0.07 (-0.09, -0.05)</b> | <b>1.59 (1.26, 1.98)</b>     |
|  | Sex <sup>†</sup>     | Male                     | -1.74 (-0.45, 3.93)                              | <b>-0.46 (-0.73, -0.17)</b> | <b>8.34 (1.33, 14.97)</b>    |
|  |                      | Ethnicity <sup>†</sup>   |  |                             |                              |
|  |                      | Pacific                  | <b>4.68 (0.42, 8.95)</b>                         | <b>-0.71 (-1.46, -0.04)</b> | 14.66 (-1.43, 33.40)         |
|  |                      | Maori                    | <b>8.16 (3.31, 13.00)</b>                        | 0.46 (-0.85, 1.03)          | <b>27.04 (6.15, 48.43)</b>   |
|  |                      | South Asian              | -2.22 (-7.17, 2.74)                              | -0.07 (-0.57, 0.18)         | -8.79 (-13.49, 6.84)         |
|  |                      | Brachial SBP (mmHg)      | -0.00 (-0.06, 0.06)                              | -0.00 (-0.01, 0.01)         | 0.00 (-0.16, 0.21)           |
|  |                      | Brachial DBP (mmHg)      | <b>0.11 (0.00, 0.22)</b>                         | -0.01 (-0.01, 0.01)         | 0.35 (-0.03, 0.59)           |
|  |                      | Augmentation index (%)   | <b>0.19 (0.10, 0.29)</b>                         | <b>0.06 (0.04, 0.07)</b>    | <b>0.38 (0.01, 0.71)</b>     |
|  |                      | EPI (mmHg.s)             | <b>0.08 (-0.57, 0.72)</b>                        | <b>0.17 (0.01, 0.24)</b>    | 1.43 (-1.80, 3.43)           |
|  |                      | Peak reservoir BP (mmHg) | -0.01 (-0.07, 0.06)                              | 0.01 (-0.00, 0.02)          | -0.03 (-0.25, 0.20)          |
|  |                      | BMI (kg/m <sup>2</sup> ) | <b>0.33 (0.09, 0.56)</b>                         | -0.01 (-0.05, 0.02)         | <b>0.89 (0.62, 1.61)</b>     |
|  |                      | Diabetes                 | -1.39 (-4.93, 2.15)                              | <b>-0.71 (-1.18, -0.07)</b> | 0.55 (-10.94, 14.70)         |
| Baroreflex<br>sensitivity<br>(ms/mmHg)                 | Age (years)          |                          | <b>-0.05 (-0.08, -0.03)</b>                      | <b>-0.03 (-0.04, -0.03)</b> | <b>-0.08 (-0.17, -0.02)</b>  |
|  | Sex <sup>†</sup>     | Male                     | 0.06 (-0.31, 0.43)                               | -0.15 (0.32, 0.02)          | 0.31 (-0.84, 1.53)           |
|  |                      | Ethnicity <sup>†</sup>   |  |                             |                              |
|  |                      | Pacific                  | 0.03 (-0.70, 0.77)                               | -0.08 (-0.36, 0.20)         | 0.29 (-1.11, 2.66)           |
|  |                      | Maori                    | 0.62 (-0.21, 1.45)                               | 0.03 (-0.46, 0.25)          | 2.35 (-0.68, 5.31)           |
|  |                      | South Asian              | 0.06 (-0.78, 0.91)                               | 0.08 (-0.17, 0.51)          | 0.42 (-1.95, 5.36)           |
|  |                      | Brachial SBP (mmHg)      | <b>-0.03 (-0.04, -0.02)</b>                      | <b>-0.01 (-0.02, -0.01)</b> | <b>-0.06 (-0.09, -0.03)</b>  |
|  |                      | Brachial DBP (mmHg)      | <b>-0.04 (-0.06, -0.03)</b>                      | <b>-0.01 (-0.02, -0.01)</b> | <b>-0.09 (-0.14, -0.05)</b>  |
|  |                      | Augmentation index (%)   | <b>0.03 (0.02, 0.05)</b>                         | <b>-0.01 (-0.01, -0.00)</b> | <b>0.13 (0.07, 0.17)</b>     |
|  |                      | EPI (mmHg.s)             | 0.11 (-0.00, 0.23)                               | -0.06 (-0.12, 0.00)         | 0.32 (-0.03, 0.67)           |
|  |                      | Peak reservoir BP (mmHg) | <b>-0.03 (-0.04, -0.02)</b>                      | <b>-0.01 (-0.02, -0.01)</b> | <b>-0.07 (-0.10, -0.04)</b>  |
|  |                      | BMI (kg/m <sup>2</sup> ) | <b>-0.06 (-0.10, -0.02)</b>                      | -0.01 (-0.02, 0.01)         | <b>-0.13 (-0.24, -0.03)</b>  |
|  |                      | Diabetes                 | -0.48 (-1.08, 0.13)                              | 0.03 (-0.14, 0.29)          | -0.73 (-2.84, 1.09)          |

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic BP; EPI, excess pressure integral; OLR, ordinary linear regression; RMSSD, root mean square of successive differences; SBP, systolic BP. All models were adjusted for age, sex ethnicity and antihypertensive use. <sup>†</sup>Reference groups for ethnicity and sex categories are “European” and “female”, respectively. 95% confidence intervals that do not encompass zero are in bold.

Figure 1

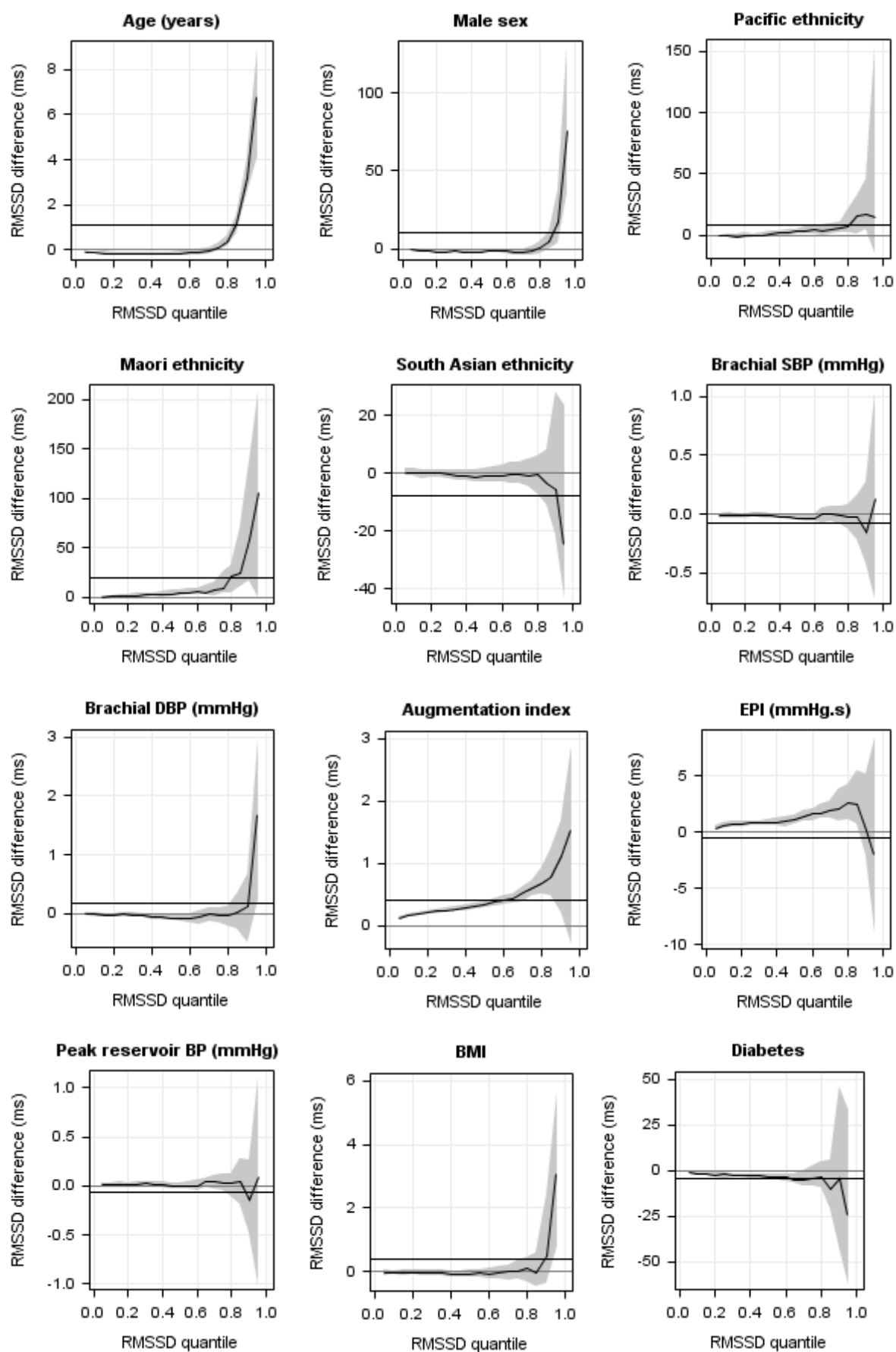


Figure 2

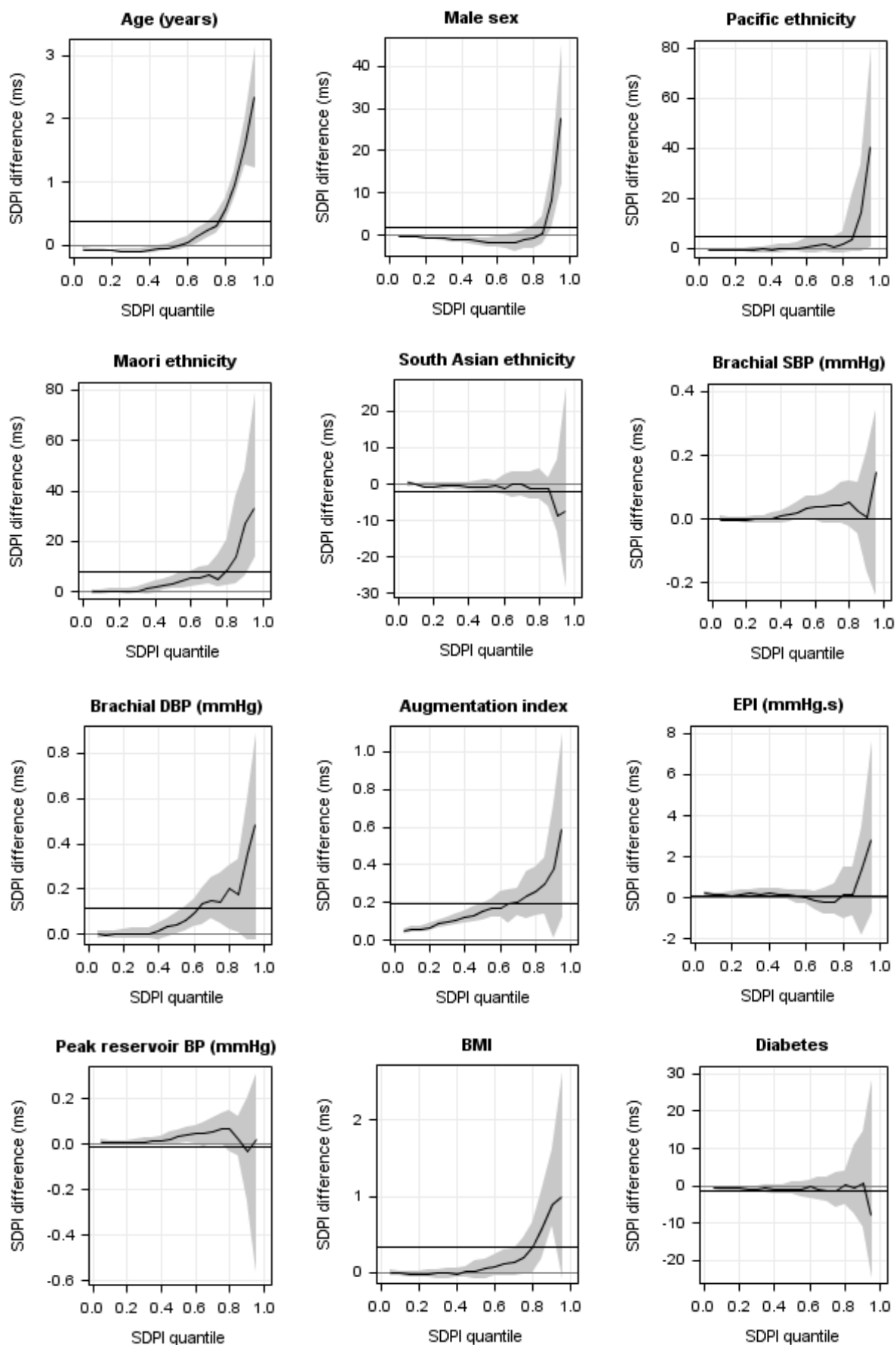




Figure 3

