Hemoglobin Level Is Positively Associated With Blood Pressure in a Large Cohort of Healthy Individuals

Femke Atsma, Ingrid Veldhuizen, Wim de Kort, Marian van Kraaij, Pieternel Pasker-de Jong, Jaap Deinum

Abstract—It has been hypothesized that an increased hemoglobin level elevates blood pressure. The present study investigated the association between hemoglobin level and systolic blood pressure and diastolic blood pressure in healthy persons. The study population was composed of 101,377 whole blood and plasma donors, who made 691,107 visits to the blood bank. At each visit, hemoglobin level and blood pressure were measured as part of the standard procedure before a blood donation. We used repeated measurement analysis to analyze the data. We used generalized estimating equation models to assess the between-person effect and linear mixed models to assess the within-person effect. All of the analyses were done separately for men and women. In the study population, 50% were men. The mean age in men was 49.3 years (±12.5 years), and in women it was 42.4 years (±13.7 years). Hemoglobin level was positively associated with both systolic and diastolic blood pressures. With respect to the between-person effect, regression coefficients for systolic blood pressure were 1.3 mm Hg per millimole per liter increase in hemoglobin level for men and 1.8 mm Hg per millimole per liter increase in hemoglobin level for women. With respect to the within-person effect, regression coefficients for systolic blood pressure were 0.7 mm Hg and 0.9 mm Hg per millimole per liter increase in hemoglobin level, for men and women, respectively. For diastolic blood pressure, results were comparable. The results show that hemoglobin level is positively associated with both systolic and diastolic blood pressures in healthy individuals. We observed consistent effects between persons but also within persons. (Hypertension. 2012;60:936-941.)

Key Words: blood pressure ▪ systole ▪ diastole ▪ hemoglobin ▪ epidemiology

Cardiovascular disease is still the leading cause of mortality in the world. According to health statistics from the World Health Organization, 17.3 million people died from cardiovascular disease in 2008, which accounts for 30% of all global deaths. Of these deaths, an estimated 7.3 million were because of coronary heart disease, and 6.2 million were because of stroke.1

Worldwide, high blood pressure is regarded as one of the most important underlying cause of cardiovascular disease.1,2 It has been reported that 54% of stroke cases and 47% of ischemic heart disease cases could be attributed to a high blood pressure.2

This substantial blood pressure--related disease burden in the population stresses the importance of maintaining blood pressure values at an adequate level. Major health benefits may be gained by decreasing blood pressure. It is estimated that substantial incidence differences in fatal and nonfatal ischemic heart disease can be observed by blood pressure differences of ≈2 to 3 mm Hg.3,4 Gaining knowledge about factors that are associated with a blood pressure increase is, therefore, imperative.

There are indications that systolic blood pressure (SBP) and diastolic blood pressure (DBP) may increase with increasing hemoglobin (Hb) levels.5,6 In previous research among hemodialysis patients, the administration of erythropoietin, an erythropoiesis-stimulating protein used for the treatment of anemia, was related to an elevated blood pressure.7,8 Moreover, in patients with orthostatic hypotension, increasing the red cell volume by erythropoietin elevated blood pressure while standing.9 In animal studies, the administration of increasing doses of cross-linked Hb during cardiopulmonary bypass surgery induced an increase in mean arterial pressure.10 Furthermore, it has also been reported that free Hb induces vasoconstriction because of NO scavenging, limiting the NO availability for vascular smooth muscle cells, which elevates the blood pressure.11,12

The presumed association between Hb level and blood pressure has been mainly investigated in patients but never in a healthy set of persons. We had the opportunity to study this effect in a large cohort of blood donors. Blood donors provide a unique and perfect study population for this type of question. Because of the application of health eligibility criteria before a blood donation, a selection process of those who are healthy...
enough to donate blood takes place. As a result, donors are composed of a relatively healthy group of individuals. In addition, the huge amount of prospectively collected donation data measured before each blood donation, including Hb levels and blood pressure, enabled us to precisely assess the strength of the association between Hb levels and blood pressure in healthy persons.

The main objective of this study was to investigate the association between Hb levels and SBP and DBP in healthy blood donors. We studied the between-person variation to observe the overall association between Hb level and blood pressure across persons. We also studied the within-person variation to observe the development of the association between Hb level and blood pressure within persons.

Methods

Study Population
The study population was composed of Dutch voluntary blood donors. The overall Dutch donor population consists of ≈400 000 donors, of whom the majority (≥97%) is of white origin. These donors provide ≈900 000 donations in the Netherlands annually. To secure both donor and blood safety, several safety measures and deferral criteria are applied according to European guidelines. Donors must be between 18 and 70 years of age and, before each blood donation, donors have to fill out an eligibility questionnaire to identify known medical conditions and perilous behavior. During the physical examination, body weight, pulse rate, blood pressure, and Hb level are measured. Eligibility criteria include a body weight ≥51 kg, regular pulse, an SBP of ≤180 mm Hg and a DBP of ≤100 mm Hg, and an Hb level of 28.4 mmol/L for men and ≤27.8 mmol/L for women.

The present study population consisted of whole blood and plasma donors who visited 1 of the 43 donation sites in the Southeast region of the Netherlands for a regular blood donation. All of the visits in the period from January 1, 2007, to December 31, 2009, were eligible for inclusion in the study. Plasma donors are allowed to donate 650 mL of plasma per donation with a maximum of 15 L of plasma a year. Whole blood donors are allowed to donate at most 3 times (women) and 5 times (men) a year, 500 mL each time. As a result, multiple visits per donor were available and used in the present study. We excluded visits with missing blood pressure measurements (n=8981) or Hb measurements (n=97). Eventually, the study data file consisted of 691 107 measurements obtained from 101 377 whole blood donors and plasma donors. The number of measurements per donor ranged from 1 to 69 in 3 years.

Data
We extracted information about Hb levels and blood pressure values from the blood bank information system (e-Progressa). During each blood bank visit, Hb level and blood pressure are recorded in this database. Hb levels are routinely measured through finger stick capillary samples using a HemoCue Hb 201 analyzer (HemoCue AB, Angelholm, Sweden). The SBP and DBP are measured once as part of routine blood bank practice, according to standardized operating procedures and in the sitting position. A digital oscillometric blood pressure monitor, type Omron HEM-907XL (Omron Healthcare) was used to obtain the blood pressure measurements. Furthermore, we retrieved the following donor characteristics from the donor data-base; date of birth, sex, length, weight, and donation type (plasma or whole blood). We calculated the body mass index (BMI) by dividing weight (in kilograms) by length squared (in meters squared). All of the variables were complete, except for BMI. In 2.5% of the donors, no length was recorded, and in 0.8% of the donors, no weight was recorded. Therefore, we used single imputation to impute missing length and weight values. To perform the single imputation, we included the variables age, sex, Hb level, SBP, DBP, donation type, and number of blood bank visits in a linear regression model with added residuals. When length was missing and weight was available, weight was also included in the model and vice versa. From these models, imputed values for length and weight were estimated.

Both Hb level and blood pressure are susceptible to seasonal variation. To explore potential confounding effects by seasonality, we retrieved climate data from the Royal Netherlands Meteorologic Institute (Volkel weather station, Southeast Netherlands). We linked these temperature data to the donation data by day.

Information about smoking and use of antihypertensive drugs, as potential confounding factors, were obtained from the Donor InSight Study. Donor InSight is a large nationwide cohort study conducted by our own research group between April 2007 and April 2009. The primary aim of Donor InSight was to describe the Dutch donor population in terms of demographics, health, and disease. Of all Donor InSight blood donors, 7056 blood donors visited the blood bank in the Southeast region. From these donors, 57 821 Hb and blood pressure measurements were available in the study period 2007–2009. In this way, we had additional information about smoking (current, former, or never smoking) and use of antihypertensive drugs (yes or no) in a subsample of blood donors, and we were able to adjust for these factors in the analyses. The Medical Ethical Committee Arnhem-Nijmegen in the Netherlands approved the Donor InSight Study. All of the donors gave written informed consent before they were included in the Donor InSight Study.

Statistical Analyses
The association between Hb level and blood pressure can be analyzed between persons and within persons. For the between-person variation we could select 1 observation per person (eg, the first), but this would lead to a considerable loss in power. Instead, we analyzed all of the repeated measurements per person, using generalized estimating equation modeling. We defined an independent correlation matrix and used robust sandwich estimators to correct for the fact that ≥1 observation per person was used. These robust sandwich estimators are smaller than the sandwich estimators that were obtained when using only 1 observation per person. In the generalized estimating equation models, SBP and DBP served as outcome measures, and Hb level was the key determinant under study. We included Hb level as a continuous variable in the model. We tested the linearity assumption by adding a quadratic term for Hb level in the model. Results from the generalized estimating equation analyses were expressed as regression coefficients with corresponding 95% CIs. We adjusted all of the regression coefficients for age, sex, BMI, and mean daily temperature, because these factors appeared to be confounding factors in the models.

Within the Donor InSight subsample we investigated the disturbing influence of antihypertensive drug use and smoking. We repeated the analyses in persons not taking antihypertensive drugs. In addition, we adjusted these generalized estimating equation coefficients for smoking.

We used linear mixed models to investigate the association between Hb level and blood pressure within persons. To do this, we first calculated a centered mean for Hb level for each person. The centered mean was calculated by subtracting each individual Hb measurement from the mean of all Hb levels within a person. By analyzing this centered mean as a fixed and random effect in the linear mixed model analyses, the within-person variation could be investigated. In linear mixed models, SBP and DBP served as outcome measures and the centered mean Hb level as the independent variable. In addition, we included a random slope for the centered mean Hb level, allowing for a person-dependent association between Hb level and blood pressure. Results from the linear mixed model analyses were expressed as regression coefficients with the standard deviation (SD) of the random slope. This SD indicates the variation in the estimated regression coefficient. Again, we adjusted all of the regression coefficients for age, sex, BMI, and mean daily temperature. All of the analyses were performed at a 2-level structure, measurements that are clustered within donors. In additional analyses, clustering of data on center level was investigated by including random effects for donation site (a 3-level approach).

We performed the analyses in the total group of 691 107 observations. In addition, we repeated the analyses in subgroups of plasma and whole blood donors. Hereto, we excluded donors who changed their donation type from whole blood to plasma donations and vice versa (4064 donors with 54 875 donations), which left 468 964 whole
Results

Baseline Characteristics

The study data file consisted of 691,107 measurements obtained from 101,377 donors (50,641 men and 50,736 women). Table 1 presents characteristics of the study population at the latest visit in the period 2007–2009. The mean age in men was 49.3 ± 12.5 years, and in women it was 42.4 ± 13.7 years. The median number of whole blood donations in this period was 6 (25th to 75th percentile, 3–10) in men and 4 (25th to 75th percentile, 2–6) in women. The median number of plasma donations was 18 (25th to 75th percentile, 10–27) in men and 12 (25th to 75th percentile, 6–20) in women. In the Donor InSight subsample, current smoking was reported by 16.1% and antihypertensive drug use by 10.1% of the donors (results not shown).

Hb Level and Blood Pressure

Between subjects, the mean SBP increased with increasing Hb level (Table 2 and Figure 1). For men, the SBP increased by 1.3 mm Hg (95% CI, 1.1–1.4 mm Hg) per millimole per liter increase in Hb level. For women, the SBP increased by 1.8 mm Hg (95% CI, 1.6–2.0 mm Hg) for each millimole per liter increase in Hb level. We observed comparable patterns for DBP (Table 2 and Figure 2). DBP rose 1.4 mm Hg (95% CI, 1.3–1.5 mm Hg) per millimole per liter increase in Hb level in men and 1.5 mm Hg (95% CI, 1.4–1.6 mm Hg) per millimole per liter Hb in women. We repeated the between-subject analyses within the Donor InSight subsample in persons not taking antihypertensive drugs and additionally adjusted these coefficients for smoking was reported by 16.1% and antihypertensive drug use by 10.1% of the donors (results not shown).

Hb Level and Blood Pressure

Between subjects, the mean SBP increased with increasing Hb level (Table 2 and Figure 1). For men, the SBP increased by 1.3 mm Hg (95% CI, 1.1–1.4 mm Hg) per millimole per liter increase in Hb level. For women, the SBP increased by 1.8 mm Hg (95% CI, 1.6–2.0 mm Hg) for each millimole per liter increase in Hb level. We observed comparable patterns for DBP (Table 2 and Figure 2). DBP rose 1.4 mm Hg (95% CI, 1.3–1.5 mm Hg) per millimole per liter increase in Hb level in men and 1.5 mm Hg (95% CI, 1.4–1.6 mm Hg) per millimole per liter Hb in women. We repeated the between-subject analyses within the Donor InSight subsample in persons not taking antihypertensive drugs and additionally adjusted these coefficients for smoking was reported by 16.1% and antihypertensive drug use by 10.1% of the donors (results not shown).
smoking. Table 3 shows that the association between Hb level and blood pressure (SBP and DBP) was still very pronounced and comparable to the effects found in the total group.

Within subjects, clear associations between Hb level and blood pressure existed as well. SBP increased with 0.7 mm Hg (SD random slope, 2.0) and 0.9 mm Hg (SD random slope, 2.1) per millimole per liter of Hb, in men and women, respectively (Table 2 and Figure 3). DBP rose 1.0 mm Hg (SD random slope, 1.2) per millimole in men and 0.9 mm Hg (SD random slope, 1.3) per millimole per liter of Hb in women (Table 2 and Figure 4). Information about stratification for different age categories is available in an online-only Data Supplement (Table S1).

The analysis with a 3-level structure showed that correction for a center effect did not materially change the variation in the slope. In both situations (with and without a random effect for donation site), the variance of the random slope was more or less the same. Therefore, including a random term for site did not change our results (results not shown). Subgroup analyses on donation type showed that results were comparable in whole blood donors and plasma donors for both SBP and DBP in men and women (results not shown).

### Table 3. Association Between Hemoglobin Level and Blood Pressure in Persons Not Taking Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Measurements</th>
<th>No. of Subjects</th>
<th>( \beta ) (95% CI) Adjusted for Age, BMI, and Mean Daily Temperature*</th>
<th>( \beta ) (95% CI) Adjusted for Age, BMI, Mean Daily Temperature, and Smoking*</th>
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<tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Men</td>
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<td>3063</td>
<td>1.3 (0.7–1.9)</td>
<td>1.3 (0.7–1.9)</td>
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<td>3283</td>
<td>1.7 (1.1–2.4)</td>
<td>1.8 (1.1–2.4)</td>
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<tr>
<td>DBP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>30 614</td>
<td>3063</td>
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<td>1.5 (1.1–1.8)</td>
</tr>
<tr>
<td>Women</td>
<td>20 711</td>
<td>3283</td>
<td>1.4 (1.0–1.8)</td>
<td>1.4 (1.0–1.8)</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

*Numbers indicate regression coefficients with corresponding 95% CIs (generalized estimating equation model) and express the increase in blood pressure in millimeters of mercury for each millimole per liter increase in hemoglobin level between persons.

### Discussion

The present study showed a positive association between Hb level and SBP and DBP in men and women. Effects were present between subjects as well as within subjects.

To our knowledge, this is the first study that investigated the association between Hb level and blood pressure in such a large cohort of healthy individuals. Some earlier cross-sectional studies also focused on the role of iron parameters in blood pressure regulation. Results of these studies were in line with findings of our study. Göbel et al found significant Pearson correlations between Hb level and arterial blood pressure in healthy persons. Furthermore, it has been reported that serum ferritin was elevated in men with essential hypertension compared with normotensive men. However, drawbacks of these earlier studies were the lack of adjustment for potential confounding factors, such as age.

The strengths of the effects reported in this study are very relevant for clinical practice. On a population level, differences of 1 to 2 mm Hg in blood pressure already mean a substantial difference in cardiovascular mortality and morbidity. In the Netherlands, it is estimated that a risk reduction of 9% to 10%
for ischemic heart disease mortality and a 12% to 14% reduction for fatal stroke can be achieved by lowering blood pressure (SBP/DBP) by 2.5/1.4 mm Hg.\textsuperscript{1} From randomized controlled trial data, it has also been estimated that an additional reduction in SBP of 2 mm Hg because of the use of newer antihypertensive drugs over older antihypertensive drugs may result in a 12% reduction of cardiovascular events and an 18% reduction of fatal and nonfatal strokes.\textsuperscript{4} These facts and our findings suggest that, in a clinical setting, hypertensive patients may benefit from donating blood by decreasing their Hb level and subsequently their blood pressure. Moreover, by understanding which physiological mechanisms contribute to both a blood pressure increase and an Hb increase, alternative approaches for blood pressure control in clinical practice may be suggested.

The mechanisms that might lead to an elevated blood pressure in individuals with an increased Hb level are not entirely known. In the past, several biological mechanisms for the Hb-blood pressure association have been proposed. It has been reported that Hb is strongly related to arterial stiffness, as measured by pulse wave velocity, which, in turn, increases SBP and DBP.\textsuperscript{9} Furthermore, free Hb may be a scavenger of NO. NO, produced in the endothelial cells that line the blood vessels, relaxes the muscle cells surrounding the vessel and thereby controls blood pressure. Increased levels of free Hb may bind to NO, which causes vessels to constrict and blood pressure to increase.\textsuperscript{31} It has also been reported that increasing molecular mass of tense-state polymerized bovine Hb has a substantial effect on vasoconstriction and blood pressure by regulating NO production.\textsuperscript{12}

An obvious mechanism for blood pressure increase with increased Hb levels would be increased blood viscosity. It has been reported that elevation of hematocrit and Hb levels increases blood viscosity and that increased viscosity partly through an effect on blood pressure may worsen cardiovascular function.\textsuperscript{22} However, other research is inconclusive about the role of blood viscosity in high blood pressure and hypertension. Studies in hypertensive patients do support the role of increased blood viscosity in raising blood pressure\textsuperscript{23} but not in healthy individuals.\textsuperscript{24} Experimentally, a study in hamsters and mice does not support the positive relationship between blood viscosity and blood pressure,\textsuperscript{25} and reduction of viscosity by isovolumichemodilution reduces blood pressure much less in normotensive than in hypertensive polycythemic patients.\textsuperscript{26} Increased blood viscosity may cause an increase in NO production and, hence, vasodilatation, through the induction of shear stress, but this is expected to offset increases in blood pressure. Because we did not measure blood viscosity and because our study included healthy persons who were mostly normotensive with normal Hb levels, we do not know if blood viscosity explains the findings of our study.

Furthermore, the administration of erythropoietin, an erythropoiesis-stimulating protein used for the treatment of anemia, has been related to an elevated blood pressure. Proposed underlying mechanisms for vasoconstriction are the presence of erythropoietin receptors on endothelial cells, increased release of serum endothelin 1 from endothelial cells, and expression of serum endothelin 1 mRNA within endothelial cells.\textsuperscript{7,8} Perhaps the effect of Hb on vasoconstriction and blood pressure runs through comparable pathways.

Finally, both Hb and blood pressure may be related to the renin-angiotensin-aldosterone system. Posttransplanterythropoietin in kidney transplant recipients can be managed by angiotensin-converting enzyme inhibitor or angiotensin receptor blocker treatment,\textsuperscript{27} and angiotensin II may play a role in erythropoietin production.\textsuperscript{24} The role of the renin-angiotensin-aldosterone system may be incited by the sympathetic nervous system, which is known to affect erythropoietin production, because subjects with autonomic neuropathy have erythropoietin-responsive anemia.\textsuperscript{29}

The present study has some strengths and limitations. The large data set and the availability of many repeated measurements per person is unique and a strong asset. The extensive amount of repeated data enabled us to estimate very precisely the association between Hb and SBP and DBP. By using sophisticated statistical methods to analyze repeated measures, we had the opportunity to distinguish the between-person variation from the within-person variation. Furthermore, we were able to adjust for the most important confounding factors, such age, sex, BMI, and mean daily temperature. In addition, we showed that smoking and antihypertensive drug use did not confound reported effects, so we argue that residual confounding is minimal in the present study.

A limitation might be the exclusion of donors from the analyses. In the subgroup analyses on donation type we excluded 54 875 donations (from 4064 donors) because of a change in donation type over time. However, we feel that leaving out these donors did not influence the results, because effect sizes in whole blood donors and plasma donors were comparable to the overall effect size. Furthermore, Hb levels and blood pressure values were measured within the same visits, which give the study a cross-sectional design. Consequently, drawing conclusions about causality is difficult. Finally, Hb values from finger stick capillary samples may be systematically different from venous Hb values. Based on our own observations, capillary Hb systematically overestimates venous Hb in the entire range with 0.3 mmol/L (data not shown). Because all Hb measurements in this study have been obtained by the same method, that is, fingerstick, according to standardized procedures, all of the measurements are systematically overestimated. Consequently, the strength of the regression coefficients and the study conclusions are not affected.

In conclusion, this study clearly shows that Hb level is positively associated with SBP and DBP in healthy individuals. We observed consistent effects between persons but also within persons. The underlying biological mechanisms for the reported associations are not yet elucidated, so reported results provide room for further mechanistic research in this field.

**Perspectives**

Results from the present study strongly add to current knowledge about factors that are associated with blood pressure. The observation of an apparent association between Hb level and both SBP and DBP in healthy persons has never been reported before and is an important novelty in hypertension research. The fact that the association was present between persons as well as within persons reinforces this observation.

Based on existing knowledge, we can only speculate about the mechanisms that underlie the association between Hb level and blood pressure. Are the same mechanisms responsible for the between-persons and within-person effects or do
different underlying pathways play a role? How is the causal pathway arranged; does Hb affect blood pressure or vice versa? Future research should therefore focus on the underlying biology, taking the causal pathway, as well as the distinction between a between-person effect and a within-person effect, into account.

Acknowledgments

We thank Dr Rogier Donders from the Department Epidemiology, Biostatistics, and Health Technology Assessment from the Radboud University Nijmegen Medical Centre in The Netherlands for providing support in the statistical analyses.

Disclosures

None.

References

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HEMOGLOBIN LEVEL IS POSITIVELY ASSOCIATED WITH BLOOD PRESSURE IN A LARGE COHORT OF HEALTHY INDIVIDUALS

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Short title: Hemoglobin level and blood pressure

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Email. f.atsma@sanquin.nl
Table S1 The association between hemoglobin level and blood pressure in different age categories

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<td>DBP*</td>
<td>1.1 (1.0-1.3)</td>
<td>1.4 (1.2-1.7)</td>
<td>1.5 (1.3-1.7)</td>
<td>1.8 (1.6-2.0)</td>
<td>1.7 (1.3-2.0)</td>
</tr>
<tr>
<td></td>
<td>Within subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>β (sd random slope)‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBP*</td>
<td>0.8 (2.0)</td>
<td>0.7 (1.9)</td>
<td>0.7 (2.4)</td>
<td>1.0 (2.5)</td>
<td>1.1 (1.3)</td>
</tr>
<tr>
<td></td>
<td>DBP*</td>
<td>0.8 (1.3)</td>
<td>0.9 (1.4)</td>
<td>0.9 (1.1)</td>
<td>0.9 (1.6)</td>
<td>0.8 (0.9)</td>
</tr>
</tbody>
</table>

* SBP, systolic blood pressure in mm Hg; DBP, diastolic blood pressure in mm Hg
† Numbers indicate regression coefficients with corresponding 95% confidence intervals (GEE) and express the increase in blood pressure in mm Hg for each mmol/L increase in hemoglobin level between persons. Regression coefficients are adjusted for age, BMI, and mean daily temperature
‡ Numbers indicate regression coefficients with the standard deviation (sd) of the random slope (LMM) and express the increase in blood pressure in mm Hg for each mmol/L increase in hemoglobin level within persons. Regression coefficients are adjusted for age, BMI, and mean daily temperature