Original Article

# Association of age-dependent height and bone mineral density decline with increased arterial stiffness and rate of fractures in hypertensive individuals

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**Objective:** Hypertension and osteoporosis are age-related health risks differentially expressed in men and women. Here we have analysed their prevalence in a randomly selected cross-sectional cohort [CARTaGENE (CaG) of Quebec, Canada and explored their existing relationships along with height, arterial stiffness and bone fractures.

**Methods:** The principal cohort CaG included 20 007 individuals of age 40–70 years. Participants were subjected to an extensive phenotyping and a questionnaire of medical history and habits.

**Results:** We determined the differences in height of participants and their relation to hypertension status and sex in this cohort and validated it in two other cohorts (The Canadian Heart Health Study and a family cohort from the Saguenay Lac Saint-Jean, a region of Quebec). In all three cohorts, we found that at younger age individuals with hypertension are taller than normotensive individuals, but they have a shorter stature at an older age compared with normotensive individuals. In CaG, we observed that hypertension, low bone mineral density (BMD) and arterial stiffness are strongly associated with height when adjusted for antihypertensive medications ($P < 0.0001$). Fractures are the net outcome of low BMD, and a significant association is observed (odds ratio = 2.34, confidence interval = 2.12–2.57); this relation was stronger in hypertensive individuals compared with normotensive individuals particularly in younger hypertensive individuals. In addition, we observed that increased arterial stiffness was significantly correlated with a low BMD in both men and women at all ages.

**Conclusion:** Shorter stature in elderly, low BMD and fractures correlated with increased arterial stiffness and hypertension. We propose that hypertension and osteoporosis share components of accelerated aging.

**Keywords:** arterial stiffness, bone mineral density, fractures, height, hypertension, men and women

**Abbreviations:** Aix, augmentation index; BMD, bone mineral density; BP, blood pressure; BUA, broadband ultrasound attenuation; CaG, CARTaGENE; CHHS, Canadian Heart Health Survey; cPP, central pulse pressure; CPTP, Canadian Partnership for Tomorrow Project; CVD, cardiovascular disease; *KCNAB1*, potassium voltage-gated channel gene; SLSJ, Saguenay-Lac St-Jean; SNP, single nucleotide polymorphism

## INTRODUCTION

Hypertension and osteoporosis are two age-related diseases that are major health burdens in Canada and worldwide. We previously proposed hypertension as a form of accelerated aging characterized by accelerated cellular turnover and faster shortening of telomere length in genetically hypertensive rats [1]. Different studies showed that hypertension is a form of accelerated growth, maturation or aging with metabolic changes and hypertrophy of the arterial wall smooth muscle cells associated with accelerated biological maturation, leading to high blood pressure (BP) and cardiovascular outcomes [2]. In addition, it was suggested from a small cohort of approximately 100 individuals that hypertensive children have an accelerated skeletal growth compared with their healthy controls [3]. McCarron *et al.* [4] reported in 1980, that hypertension is associated with abnormal calcium metabolism, including an increase in calcium excretion for a given sodium intake, and an increase in parathyroid gland activity. In the last decade, many studies tried to unveil the existing relation between hypertension and osteoporosis in animal models and in humans [5,6]. The direct association between these two diseases in a large

Journal of Hypertension 2015, 33:727–735

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**Received** 6 June 2014 **Revised** 30 October 2014 **Accepted** 30 October 2014



DOI:10.1097/HJH.0000000000000475

population-based study has not yet been reported. However, a small study by Tsuda *et al.* [7] on 31 hypertensive and 14 normotensive Japanese women showed that the bone mineral density (BMD) in the lumbar spine was inversely correlated with SBP. In addition, the 24-h urinary calcium excretion was increased compared with normotensive individuals. In a large case–control study, Vestergaard *et al.* [8] assessed the impact of hypertension and other cardiovascular diseases (CVDs) on the risk of fractures and observed that hypertension and stroke were important independent cardiovascular risk factors for fractures. Andreassen *et al.* [9] recently identified common genetic variants of BP that are associated with other phenotypes. Among the significant single nucleotide polymorphisms (SNPs) that were associated with SBP were those associated with BMD and height. In previous studies that we conducted with the Canadian Heart Health Study (CHHS) and the family cohort of the Saguenay Lac-St Jean area, we noticed an age-dependent difference in body height between hypertensive and normotensive individuals [10]. Our current analysis was performed in a population-based cohort, 'CARTaGENE' (CaG). It represents a random sample of Quebec's population and included 9628 men and 10 261 women. Our objective was to explore the notion that hypertension is a form of accelerated ageing and to search for the potential relation between four ageing processes: hypertension, arterial stiffness, short stature and low BMD resulting in fractures.

# METHODS

## Participants

CaG is a population-based cohort established in 2003 in Quebec (Canada). It includes 20 007 randomly selected individuals age between 40 and 70 years. Available data analysed here are from 19 889 individuals including 9628 men and 10 261 women evaluated during August 2009 and October 2010. The recruitment of participants and study design of CaG were recently described [11]. Ethics approval was granted by the Faculty of Medicine of the University of Montreal and the ethical research committee of the CHUM Research Center.

Data from two other cohorts were used to study the relation between hypertension status and height analyses: the population health survey CHHS and 120 families of the Saguenay-Lac St-Jean (SLSJ) population of Quebec (French Canadians).

Canadian Heart Health Survey (CHHS) is a study that included random sample of participants from 10 Canadian provinces from 1986 till 1992. A total of 23 129 individuals from 18 to 74 years old participated in the study: body height, BP and weight were obtained among other physical measurements [12].

One hundred and twenty extended families from the SLSJ population of Quebec residing in a relatively isolated region for whom genealogical records dating to the seventeenth century are available. Those families were ascertained by the presence of a sibpair affected with early-onset of hypertension and/or dyslipidemia. Anthropometric measurements including body height from 849 participants' (older than 18 years) were used in the current analysis [10].

## Health questionnaire

CaG used a standardized validated interviewer-based questionnaire, in addition to a self-administered questionnaire answered by all participants. The interviewer-based questionnaire covered health and medical history and included a detailed history of diagnosis of hypertension and osteoporosis among other diseases. The prescribed medications administered to the participants were all recorded from the packaging in addition to all other supplements taken without prescription.

## Procedures

For each set of data collection, a specialized phenotype committee was established and corresponding standard operating procedures were developed. All procedures were tested in a pilot study of 223 participants and personnel were trained accordingly. Twelve assessment sites in Québec studied the same physical measurements and questionnaires. All procedures were performed according to the standard operating manual either as previously reported by Kotchen *et al.* [13] or as described by Awadalla *et al.* [11].

## Peripheral blood pressure

Peripheral BP was measured using an Omron IntelliSense BP Monitor (HEM-907XL; Omron Healthcare, Inc., Lake Forest, Illinois, USA). Appropriate cuff size was applied to the nondominant arm, with the participant in a sitting position. The readings started 10 min after being seated and three measurements were taken 5 min apart. The mean of all available BP measures was used. Hypertension was defined as a mean SBP at least 140 mmHg, and/or a mean DBP at least 90 mmHg, and/or being treated for hypertension [14].

## Applanation tonometry

After peripheral BP measurement, the same arm was used for applanation tonometry recording. A micromanometer-tipped probe (SphygmoCor; AtCor Medical Pty Ltd, West Ryde, New South Wales, Australia) was applied at the surface of the skin overlying the radial artery and a continuous recording of the peripheral radial pulse wave form was carried for 5 min. The methodological details of this measurement were described by Siebenhofer *et al.* [15] Augmentation index (Aix) in percentage, an indirect measure of arterial stiffness, was calculated as follows: (augmentation pressure/pulse pressure) × 100 [16].

## Bone mineral density

BMD was measured on the calcaneus bone using the Lunar Achilles Insight/Express (GE Medical Systems Lunar, Madison, Wisconsin, USA). The Achilles Quantitative Ultrasound System measures the speed of sound and the frequency-dependent broadband ultrasound attenuation (BUA) and combines them to form a clinical measure. The Achilles Express device includes a mould where the heel and the malleolus are properly positioned. The foot was measured in a standardized way, and it was immobilized by a toe peg that was fixed between the big and the second toe to limit any movement of the foot. *t*-Score is

used by physicians to diagnose osteoporosis as proposed by the World Health Organization. *t*-Scores are expressed in standard deviation units and are represented in different ranges: above −1 is considered as 'normal', from −1 to −2.5 is considered as 'osteopenia' and below −2.5 as 'osteoporosis' [17]. The low BMD group included the osteopenic and osteoporotic categories and those individuals taking antiosteoporotic medications.

### Height

Height was measured without shoes, using the Seca 214 Stadiometer (graduation: 1 mm) (Seca North America, Chino, California, USA) Three repeated measures were taken, and their average was used in the current study.

### Statistical analysis

The analyses were performed using SAS 9.2 (SAS Institute Inc. Cary, North Carolina, USA). A total of 18 347 participants had nonmissing data for bone and hypertension phenotype analysis, whereas 13 471 participants had interpretable data for arterial stiffness. Descriptive statistics such as numbers, proportions for categorical variables, means and standard error of the mean for continuous variables were used. Analysis of variance was used for continuous variables. Logistic regressions were used for categorical variables and odds ratio was calculated. Simple linear regression was used to assess the association between continuous variables. The significance threshold was fixed at 0.05.

## RESULTS

### General description

CaGs participants (31.8%) were hypertensive individuals, with mean SBP and DBP of $136 \pm 17$ and $79 \pm 12$ mmHg, respectively (Table 1 and Supplement B and C). In this cohort, 18.3% had a low BMD and 13.1% had fractures (Table 1). When we separated the participants according to their BP status, age and sex, we observed that younger hypertensive individuals had a higher prevalence of low BMD and fractures compared with normotensive individuals (Supplement A). We observed no significant difference in the older age groups between hypertensive and normotensive individuals.

### Body height

We have previously reported the incidence of hypertension in Canada [12]. Here we have further explored its relationship with height. We investigated the differences in height between hypertensive and normotensive individuals in three independent cohorts, first in the CHHS and observed that hypertensive individuals were taller before the age of 50 and had a shorter stature after that age compared with normotensive individuals in both men and women; the slope of decline was significantly steeper in hypertensive compared with normotensive individuals (slope difference in men $P = 0.0032$; slope difference in women $P = 0.0012$) (Fig. 1). A second analysis was performed in the family cohort of the SLSJ population of Quebec [10]. The analysis showed that hypertensive individuals from the same families were taller before the age of 36 compared with their normotensive siblings and were shorter after that age. This relation was true in both sexes (slope difference in men $P = 0.0175$, slope difference in women $P = 0.0321$) (Fig. 1). We then performed the same analysis in CaG, which includes only participants older than 40 years of age, and observed that older hypertensive men and women were shorter than normotensive individuals (Fig. 1). Although the slope was significantly different only in men, women

**TABLE 1. Description of categorical variables (CARTaGENE, *N* = 18 347)**

| | All<br>% (*N*) | Normotensive individuals<br>% (*N*) | Hypertensive individuals<br>% (*N*) |
|---|---|---|---|
| | 100 (18 347) | 100 (12 510) | 100 (5837) |
| Age group (years) | | | |
| 40–54 | 58.3 (10 694) | 67.1 (8394) | 39.4 (2300) |
| 55–70 | 41.7 (7653) | 32.9 (4116) | 60.6 (3537) |
| Sex | | | |
| Men | 48.5 (8898) | 44.5 (5566) | 57.1 (3332) |
| Women | 51.5 (9449) | 55.5 (6944) | 42.9 (2505) |
| BMD | | | |
| Normal | 81.7 (14 991) | 82.9 (10 370) | 79.2 (4621) |
| Low BMD | 18.3 (3356) | 17.1 (2140) | 20.8 (1216) |
| Bone fractures | | | |
| No | 86.9 (15 945) | 87.9 (11 000) | 84.7 (4945) |
| Yes | 13.1 (2402) | 12.1 (1510) | 15.3 (892) |
| Antihypertensive medications | | | |
| No | 79.9 (14 654) | 100 (12 510) | 36.7 (2144) |
| Yes | 20.1 (3693) | 0 | 63.3 (3693) |
| Osteopenia medications | | | |
| No | 76.3 (14 002) | 77.3 (9672) | 74.2 (4330) |
| Yes | 23.7 (4345) | 22.7 (2838) | 25.8 (1507) |
| Osteoporosis medications | | | |
| No | 96.5 (17 710) | 96.9 (12 125) | 95.7 (5585) |
| Yes | 3.5 (637) | 3.1 (385) | 4.3 (252) |

BMD, bone mineral density.

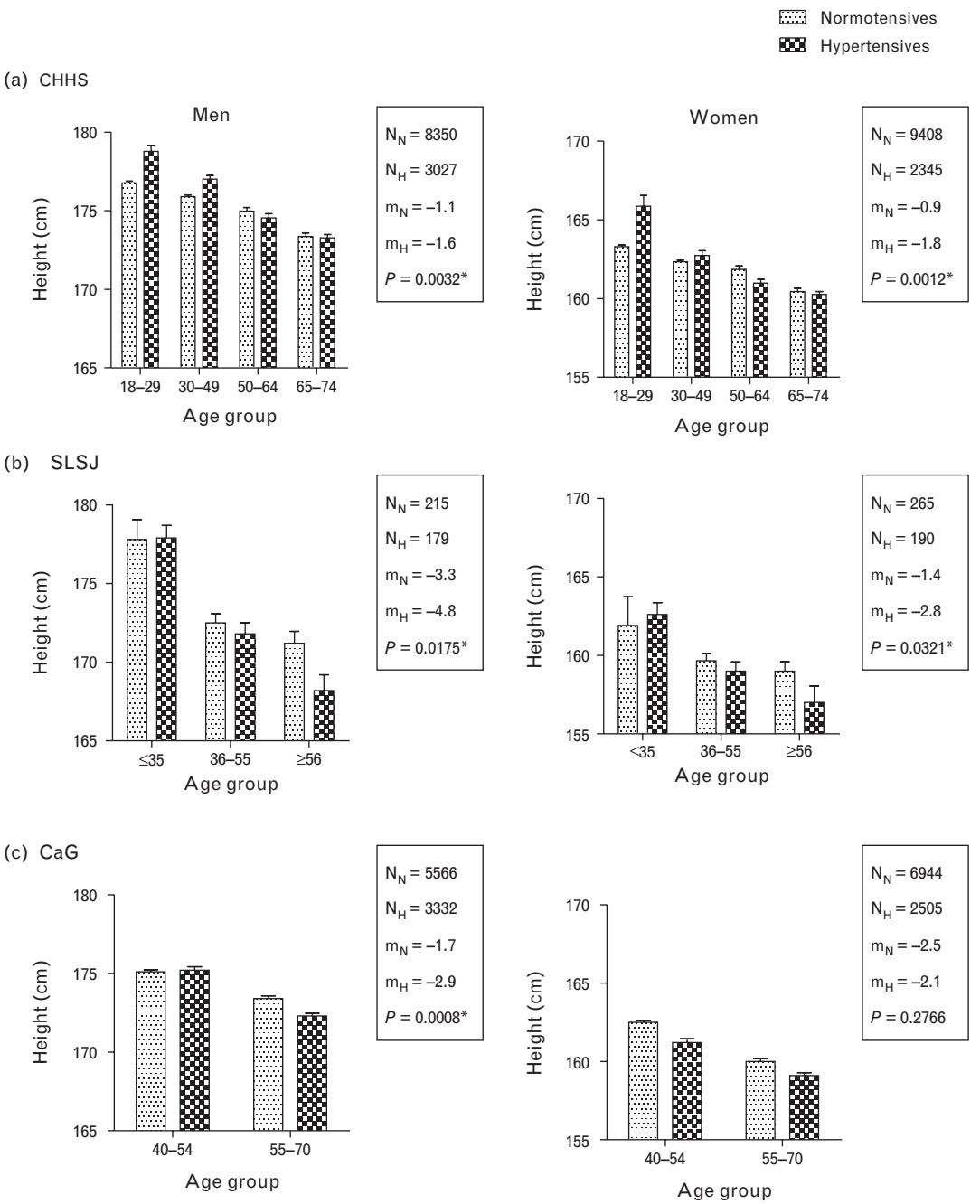


**FIGURE 1** Height in normotensive and hypertensive individuals in (a) Canadian Heart Health Study (CHHS) ($N = 23\,129$), (b) Family cohort of the French Canadians (SLSJ) ($N = 849$), (c) CARTaGENE (CaG) ($N = 18\,347$). $N_N$ (number of normotensive participants); $N_H$ (number of hypertensive participants); $m_N$ (slope of height in normotensive participants); $m_H$ (slope of height in hypertensive participants), the significance threshold for $P$ value was set at 0.05.

were already shorter at the younger age as reported in Table 2. The significant difference of slopes observed in hypertensive individuals compared with normotensive was also seen in nontreated and in treated hypertensive participants in the CHHS and CaG (Supplement D and E).

## Bone, body height and blood pressure parameters

To understand the decrease in height of hypertensive individuals with age, we investigated the relation between height, bone density (BUA) and BP parameters including arterial stiffness in the CaG study. Our association analysis showed that among the cardiovascular parameters, the Aix (a surrogate of arterial stiffness) had the most significant association with height ($P < 0.0001$), and it contributed to 20% of height changes ($R^2 = 0.20$). This association was found to be true in both men and women at all ages (Table 3). We then considered whether the decrease in body height is due to BMD loss. The association between BUA and height was significant ($P < 0.0001$) and contributed to 4% of height changes observed ($R^2 = 0.04$). BUA and height were significantly correlated in younger men (age group 40–54 years) and in women (all age groups) (Table 3).

**TABLE 2. Mean of height in men and women according to blood pressure status in CARTaGENE**

| | Normotensive individuals Mean (SD) (cm) | Hypertensive individuals Mean (SD) (cm) | *P* |
|---|---|---|---|
| 40–54 years | | | |
| Men | 175.2 (6.5) | 175.2 (6.5) | 0.9448 |
| Women | 162.4 (6.1) | 161.3 (6.0) | <0.0001 |
| 55–70 years | | | |
| Men | 173.4 (6.5) | 172.4 (6.5) | <0.0001 |
| Women | 159.9 (5.9) | 159.0 (6.0) | <0.0001 |

SD, standard deviation.

## Association of hypertension and bone fractures

The association of height with hypertension, on one hand, and with low BMD, on the other, led us to assess the possible relationship between hypertension and low BMD. We therefore examined the prevalence of low BMD among hypertensive and normotensive individuals. We observed that 17.1 and 12.1% of normotensive and 20.8 and 15.3% of hypertensive individuals ($P < 0.0001$) had a low BMD and fractures, respectively (Table 1). The higher rate of low BMD and fractures persist despite the significantly higher osteoporotic treatment received by hypertensive individuals compared with normotensive ($P < 0.0001$). Bone fracture has always been known to be the result of a low BMD, in CaG we observed a significant relation between low BMD and fractures (odds ratio = 2.34, CI = 2.12–2.57). This relation was increased in hypertensive compared with normotensive individuals in both sexes and at all ages (Table 4).

## Bone and cardiovascular parameters

We then analysed available peripheral and central parameters of BP and assessed their potential association with BUA. We observed that Aix, central and peripheral pulse pressure (cPP and PP), respectively, were inversely associated with BUA ($P < 0.0001$), indicating a decreased BMD with the increase in central and peripheral BP parameters when adjusted for antihypertensive medications (Table 5). The relation between arterial stiffness and BUA remains even after stratification for age and sex, with risk of fracture more pronounced among hypertensive individuals of both sexes, particularly at younger age of 40–54 years (Table 6). The different classes of antihypertensive medications did not exert a significant effect on the association of BUA and the cardiovascular parameters. We observed the same negative association between BUA, Aix, cPP and PP, with Aix having the highest association with BUA (Supplement F). Other concerns that might affect this association are height, weight, BMI and age among other parameters; we therefore analysed their relation with BUA [18,19]. Our analysis showed that BUA is most significantly associated with BMI ($\beta = 0.56$, $P < 0.0001$) than to height ($\beta = 0.32$, $P < 0.0001$) or weight ($\beta = 0.23$, $P < 0.0001$). Therefore, we further adjusted BUA for BMI, age, sex, antihypertensive and osteoporotic medications and the negative association between BUA and the different cardiovascular parameters was maintained (Table 7).

# DISCUSSION

CaG study is both a population-based biobank and the largest ongoing prospective health study of men and women in Quebec (Canada). The importance of this cohort

**TABLE 3. Linear regression with height as dependent variable**

| | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted data | | | Adjusted data | | | Unadjusted data | | | Adjusted data | | |
| | β | SE (β) | *P* | β[a] | SE (β) | *P* | β | SE (β) | *P* | β[a] | SE (β) | *P* |
| 40–54 years | | | | | | | | | | | | |
| Hypertension (1/0) | −0.21 | 0.27 | 0.4295 | −0.14 | 0.21 | 0.9448 | −1.35 | 0.33 | <0.0001 | −1.03 | 0.21 | <0.0001 |
| BUA | 0.01 | 0.00 | 0.0181 | 0.02 | 0.01 | 0.0171 | 0.04 | 0.00 | <0.0001 | 0.04 | 0.00 | <0.0001 |
| pDBP (mmHg) | −0.02 | 0.01 | 0.0075 | −0.02 | 0.27 | 0.3184 | −0.04 | 0.01 | <0.0001 | −0.04 | 0.01 | <0.0001 |
| pSBP (mmHg) | −0.01 | 0.01 | 0.1213 | −0.01 | 0.01 | 0.1071 | −0.03 | 0.00 | <0.0001 | −0.04 | 0.00 | <0.0001 |
| pPP (mmHg) | −0.01 | 0.01 | 0.4327 | −0.01 | 0.01 | 0.4504 | −0.03 | 0.01 | 0.0038 | −0.03 | 0.01 | 0.0064 |
| cDBP (mmHg) | −0.03 | 0.01 | 0.0025 | −0.03 | 0.01 | 0.0022 | −0.05 | 0.01 | <0.0001 | −0.05 | 0.01 | <0.0001 |
| cSBP (mmHg) | −0.05 | 0.01 | <0.0001 | −0.05 | 0.01 | <0.0001 | −0.05 | 0.01 | <0.0001 | −0.05 | 0.01 | <0.0001 |
| cPP (mmHg) | −0.09 | 0.01 | <0.0001 | −0.09 | 0.01 | <0.0001 | −0.07 | 0.01 | <0.0001 | −0.08 | 0.01 | <0.0001 |
| Aix (%) | −0.16 | 0.01 | <0.0001 | −0.16 | 0.01 | <0.0001 | −0.12 | 0.01 | <0.0001 | −0.12 | 0.01 | <0.0001 |
| 55–70 years | | | | | | | | | | | | |
| Hypertension (1/0) | −1.13 | 0.29 | 0.0001 | −1.00 | 0.21 | <0.0001 | −0.55 | 0.31 | 0.0736 | −0.95 | 0.19 | <0.0001 |
| BUA | 0.01 | 0.01 | 0.0800 | 0.01 | 0.01 | 0.0993 | 0.04 | 0.01 | <0.0001 | 0.04 | 0.07 | <0.0001 |
| pDBP (mmHg) | 0.00 | 0.01 | 0.7492 | −0.01 | 0.01 | 0.6034 | −0.01 | 0.01 | 0.0771 | −0.01 | 0.01 | 0.1419 |
| pSBP (mmHg) | −0.03 | 0.01 | <0.0001 | −0.03 | 0.01 | <0.0001 | −0.02 | 0.00 | <0.0001 | −0.03 | 0.00 | 0.0010 |
| pPP (mmHg) | −0.05 | 0.01 | <0.0001 | −0.05 | 0.01 | <0.0001 | −0.03 | 0.01 | 0.0001 | −0.02 | 0.01 | 0.0013 |
| cDBP (mmHg) | 0.00 | 0.01 | 0.9875 | 0.00 | 0.01 | 0.8225 | −0.02 | 0.01 | 0.0953 | −0.01 | 0.01 | 0.1607 |
| cSBP (mmHg) | −0.04 | 0.01 | <0.0001 | −0.04 | 0.01 | <0.0001 | −0.04 | 0.01 | <0.0001 | −0.03 | 0.01 | <0.0001 |
| cPP (mmHg) | −0.09 | 0.01 | <0.0001 | −0.08 | 0.01 | <0.0001 | −0.06 | 0.01 | <0.0001 | −0.05 | 0.01 | <0.0001 |
| Aix (%) | −0.12 | 0.01 | <0.0001 | −0.12 | 0.01 | <0.0001 | −0.09 | 0.01 | <0.0001 | −0.10 | 0.01 | <0.0001 |

BUA, broadband ultrasound attenuation; SE, standard error.
[a]Hypertension, peripheral DBP (pDBP), peripheral SBP (pSBP), peripheral pulse pressure (pPP), central DBP (cDBP), central SBP (cSBP), central pulse pressure (cPP), augmentation index (Aix) coefficients are adjusted for antihypertensive medications. BUA coefficients are adjusted for antiosteoporotic and antihypertensive medications.

**TABLE 4. Logistic regression with fractures as a dependent variable and bone mineral density status as an independent variable separated by age, sex and blood pressure status**

| | Normotensive participants | | | | Hypertensive participants | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| | OR | CI | OR | CI | OR | CI | OR | CI |
| 40–54 years Low BMD | 1.54 | 1.13–2.08 | 2.20 | 1.67–2.87 | 2.36 | 1.51–3.60 | 2.81 | 1.73–4.49 |
| 55–70 years Low BMD | 2.04 | 1.51–2.73 | 1.84 | 1.51–2.25 | 2.10 | 1.59–2.77 | 1.54 | 1.20–1.98 |

BMD, bone mineral density, CI, confidence interval; OR, odds ratio.

resides in the presence of physical measurements data, including parameters such as BMD and arterial stiffness. In 1990, the prevalence of hypertension in Quebec's population was 20.8% [20] and rose to 31.8% 10 years later (from CaGs data). In Canada, the prevalence of hypertension was 22% in 1997 [12] and was reported to be 19% 10 years later (the Canadian Health Measures Survey 2007–2009) [21]. This apparent high prevalence in Quebec in the last decade could be explained by different environmental components such as lifestyle, dietary intake, obesity and other factors, yet in the Canadian Health Measures Survey, the BP determination was done using the BpTRU device where the first reading was omitted. As the first measurement is generally higher in this procedure, the decrease in the estimate of hypertensive individuals in Canada observed in the 2007–2009 period could have been overestimated, and the real prevalence not diminished [22].

We previously suggested that hypertension is a form of accelerated ageing [1]. Observations concerning the height of hypertensive individuals compared with normotensive, from two previous studies in which we participated (CHHS and SLSJ) led us to hypothesize of the potential relation between hypertension and height, two traits affected by ageing. We therefore investigated this relation in all three cohorts. In the CHHS and SLSJ we found that hypertensive individuals are taller than normotensive individuals at a younger age, but display a lower body height in elderly, suggesting a more rapid decrease of height as compared with normotensive individuals. A genetic finding that could explain this height difference is the SNP rs1874952 that resides within the potassium voltage-gated channel gene (*KCNAB1*) that we found to be linked and associated with adult height in hypertensive individuals only (http://www.pulsus.com/ccc2010/abs/065.htm). This channel is present in osteoclasts and can regulate their activity. In addition, *KCNAB1* gene was reported to contribute to the osseographic scoring system in the Framingham study [23]. In a study done by Valverde *et al*. [24] it was shown that the blockade of the potassium-gated channels reduces the osteoclastic activity and thus reduces bone resorption. Accelerated aging, the SNP association with height in hypertensive individuals and the regulated activity of osteoclasts by the *KCANB1* gene explains an important part of the mechanism underlying the association of height and BUA. In CaG, we observed a shorter stature of elderly hypertensive individuals compared with elderly normotensive individuals. This incited us to question whether this could be due to bone loss, and our analysis confirmed a significant association of height and BUA decline with age, more pronounced in hypertensive individuals. A common fact that is observed in the aging population worldwide is height decline with age. Height measurements are usually used to assess the socioeconomic status of a population, for example childhood nutrition status, the disease environment, and the like. [25]. Other studies unveiled the relation between height decline and bone loss. A study performed by Galloway *et al*. [26] on 1024 individuals (735 women and 289 men) evaluated the correlation between height decline and bone loss with ageing. Their findings show that BMD plays the largest role in determining annual height reduction. In a cross-sectional study done on participants from the Malaysian Aging Men Study, 840 individuals were recruited with a mean age of 47.3 years. Bone density measured on the calcaneus bone using the quantitative ultrasound system, the speed of ultrasound [speed of sound (SOS)] was used in their analysis. It was shown that height was only negatively correlated with SOS in middle-aged and older men but not in younger men indicating the decrease in bone density and height with age in men [19]. Although height is negatively associated with BUA,

**TABLE 5. Linear regression with broadband ultrasound attenuation as dependent variable and cardiovascular parameters as independent variables**

| | Unadjusted data | | | Adjusted data | | |
|---|---|---|---|---|---|---|
| | β | SE (β) | *P* | β[a] | SE (β) | *P* |
| PP | −0.05 | 0.01 | <0.0001 | −0.04 | 0.01 | <0.0001 |
| cPP | −0.13 | 0.01 | <0.0001 | −0.11 | 0.01 | <0.0001 |
| Aix | −0.19 | 0.01 | <0.0001 | −0.17 | 0.01 | <0.0001 |

SE, standard error.
[a]pulse pressure (PP), central pulse pressure (cPP), augmentation index (Aix) coefficients are adjusted for antihypertensive medications.

**TABLE 6. Linear regression with broadband ultrasound attenuation as dependent variable and cardiovascular parameters as independent variables separated by age and sex**

| | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted data | | | Adjusted data | | | Unadjusted data | | | Adjusted data | | |
| | β | SE (β) | *P* | β[a] | SE (β) | *P* | β | SE (β) | *P* | β[a] | SE (β) | *P* |
| 40–54 years | | | | | | | | | | | | |
| PP | −0.00 | 0.02 | 0.9733 | −0.00 | 0.02 | 0.9067 | −0.08 | 0.02 | 0.0004 | −0.08 | 0.02 | 0.0005 |
| cPP | −0.03 | 0.03 | 0.2147 | −0.03 | 0.03 | 0.1805 | −0.11 | 0.03 | <0.0001 | −0.10 | 0.02 | <0.0001 |
| Aix | −0.07 | 0.02 | 0.0008 | −0.07 | 0.02 | 0.0010 | −0.10 | 0.02 | <0.0001 | −0.10 | 0.02 | <0.0001 |
| 55–70 years | | | | | | | | | | | | |
| PP | −0.05 | 0.02 | 0.0276 | −0.04 | 0.02 | 0.0431 | −0.09 | 0.02 | <0.0001 | −0.08 | 0.02 | <0.0001 |
| cPP | −0.06 | 0.02 | 0.0071 | −0.05 | 0.02 | 0.0131 | −0.10 | 0.02 | <0.0001 | −0.09 | 0.02 | <0.0001 |
| Aix | −0.06 | 0.02 | 0.0181 | −0.06 | 0.02 | 0.0145 | −0.05 | 0.03 | 0.0330 | −0.06 | 0.02 | 0.0213 |

Aix, augmentation index; cPP, central pulse pressure; PP, pulse pressure; SE, standard error.
[a]Cardiovascular parameters coefficients are adjusted for antiosteoporotic and antihypertensive medications.

a limitation in our study is that we cannot judge from our data whether it is also due to vertebral fractures that are however also attributable to osteoporotic process [27–29]. It is known that vertebral fractures result in important height loss, and sometimes patients have an asymptomatic vertebral fracture [30]. In this study, we show that elderly hypertensive individuals are shorter, have a lower BMD and a higher reported rate of fractures than elderly normotensive individuals, which suggests a certain form of accelerated aging observed in hypertensive individuals. In addition, our observation suggests that hypertensive individuals should be particularly studied as they lose body height and have low BMD faster than their normotensive counterparts.

It is of clinical significance that relation between hypertension and BMD result in an increase prevalence of fractures in hypertensive individuals. The results of other studies are in agreement with our observations, such as the cross-sectional analysis published by Wada *et al.* [31] on Japanese women that showed a significantly higher prevalence of hypertension in women with vertebral fractures compared with those without fractures. A study done by Sennerby *et al.* [32] on 31 936 Swedish twins showed that the diagnosis of CVD was significantly associated with an increased risk of hip fractures. This suggests the presence of shared determinants underlining CVD and the high risk of hip fractures. In a recent publication that covered many different experimental and clinical studies, it was suggested that CVD and osteoporosis are significantly associated [33]. In addition, Andreassen *et al.* [9] observed a set of common SNPs between BP and BMD for the *IKBKAP*, *NMT1* and *PLCD3* genes, which could represent the link between those two phenotypes. Different metabolic disorders such as calcium handling that are seen in these two diseases may explain some of the pathophysiological features of the link [7]. A cross-sectional study carried out by Varenna *et al.* [34] describes the coexistence of hypertension and osteoporosis and the impact of low dairy intake on the increased association of these two diseases. Despite the accumulating evidence of the link between these two age-related diseases, no official guidelines were set to be put in clinical practice. The rates of low BMD and fractures often increase with age, in our data in the age group of 40–54 years there was 11.9 and 9% of low BMD and fractures compared with 27.3 and 18.8%, respectively, in the older age group (55–70 years). The increased rate of low BMD and fractures in hypertensive individuals compared with normotensive individuals was more pronounced in younger individual, in accordance with our hypothesis of the early aging. This difference is attenuated at older age in which the bone disorder is present even without hypertension. This is compatible with genetic influence, more evident at younger age with environment overriding later.

In our current data, we unveiled that Aix, a marker of arterial stiffness was significantly associated with height, and it contributed to 20% of height differences. A study done by Reeve *et al.* [35] showed that taller people have better central haemodynamics and reduced cardiovascular risks. Ageing leads to various changes in the cardiovascular system including the augmentation in arterial stiffness and in PP; therefore, high Aix and cPP are good indicators of aged vasculature and an increased arterial stiffness [36]. It is held that peripheral PP is a strong predictor of heart attack and stroke, and it is often assumed that it reflects the central

**TABLE 7. Linear regression with broadband ultrasound attenuation as dependent variable and cardiovascular parameters as independent variables**

| | Unadjusted data | | | Adjusted data | | |
|---|---|---|---|---|---|---|
| | β | SE (β) | *P* | β[a] | SE (β) | *P* |
| PP | −0.05 | 0.01 | <0.0001 | −0.02 | 0.01 | 0.0244 |
| cPP | −0.13 | 0.01 | <0.0001 | −0.03 | 0.01 | 0.0287 |
| Aix | −0.19 | 0.01 | <0.0001 | −0.04 | 0.01 | 0.0023 |

Aix, augmentation index; cPP, central pulse pressure; PP, pulse pressure; SE, standard error.
[a]Cardiovascular parameters coefficients' are adjusted for BMI, age, sex, antiosteoporotic and antihypertensive medications.

PP. In 2006, the Conduit Artery Function Evaluation (CAFÉ) study challenged that notion and showed that two BP-lowering drugs had a similar impact on brachial BP but had a significantly different impact on reducing central aortic PP [37]. Those studies revealed the importance of cPP and its ability to better predict cardiovascular events (such as heart attacks and stroke). A recent study showed that arterial stiffness is associated with an increase in BP over time and is a good clinical marker for hypertension progression [38]. Moreover, in our study we observed a significant inverse association between arterial stiffness and BUA. Mangiafico *et al.* [39] showed in a study in which hypertensive women were excluded, that postmenopausal women with osteoporosis have an increased Aix and cPP in a small set of 182 osteoporotic and 160 controls, in spite of equal peripheral pressure. Another small study carried by Sumino *et al.* [40] showed the increased arterial stiffness in 25 osteoporotic postmenopausal women. BUA measured by the quantitative ultrasound system reflects BMD; thus, in our study the inverse association between parameters of arterial stiffness and BUA in a large population-based cohort, and most importantly in both sexes, largely validates initial small studies in patients with demonstrated osteoporosis. It is suggested that different parameters could affect the values of BUA, such as age, weight, height, the presence of different assessment centres, and others [18,41]. In this study we show that the relation between Aix and BUA remained the same even after adjustment for BMI, age, sex, antihypertensive and osteoporotic medications, implying the strong association between these parameters. This further suggests that low BMD and an increased central BP are part of an accelerated aging process that would normally occur in elderly but is not searched for in young hypertensive individuals.

Some showed the importance of calculating the coefficient of variation to avoid the repositioning problems in participants in case more than one measurement is taken [18]. Another study reported variability of the hip measurement between different recruiting centres [27]. In CARTaGNE, all the assessment sites followed a standardized procedure for BUA measurement, and it was only carried one time for each individual; we therefore could not calculate the coefficient of variation. But as all centres used the same instrument and standard operating procedures and all the personnel were well trained and monitored increased our confidence in the data as presented.

To our knowledge we are the first to show, in two population cohorts and one family cohort, the dynamics of age-dependent association between hypertension and height. In addition, the novelty of this study resides in the size of this cross-sectional population cohort and the hypertensive and osteoporotic phenotypes that were gathered such as arterial stiffness and BMD in men and women. Our study presents a new opportunity to search for clinically relevant osteopenia in hypertensive men and women. The preventive intervention for progression of both arterial stiffness and fractures remains to be explored. The United States Preventive Services Task Force recommends screening for osteoporosis in women of 65 years of age or older and in women who have fractures that represent a high-risk factor. The United States Preventive Services Task Force concludes that the current evidences are insufficient to screen for osteoporosis in men. On the basis of our results, we propose that such evaluation may be warranted in men with hypertension to prevent the increase of fractures in this disease.

In conclusion, considering the association of decreasing height and bone density associated with increased arterial stiffness and rate of fractures, our study indicates that hypertension and osteoporosis are forms of accelerated aging sharing at least in part its pathophysiological processes. Furthermore, our data unveil the potential relevance of evaluating bone health in hypertensive men.

## ACKNOWLEDGEMENTS

The authors thank the funding agencies: The Canadian Institute for Health Research (CIHR), Genome Quebec, Genome Canada and Canadian Partnership for Tomorrow Project (CPTP), and acknowledge the contribution of the volunteers who participated in the three cohorts.

This study was supported by the Canadian Institute for Health and Research (CIHR), Genome Quebec, Genome Canada and Canadian Partnership for Tomorrow Project (CPTP).

P.H. was the senior investigator of this study and for the Saguenay Lac Saint-Jean study. R.E.-B. was the principal executer of the study. R.T. was the statistical consultant. J.T, P.D., O.Š., L.Š. and L.-G.S.-M. were advisors for this study. C.L., B.M.-K. and P.A. were the principal investigators for CARTaGENE. P.H. was the medical director for CARTaGENE. M.J. was the principal investigator of the Canadian Heart Health Measure Survey. D.G. was a coinvestigator of the Family cohort of the Saguenay Lac St-Jean. R.E.-B. drafted the manuscript and all authors contributed to its revision and approved its final version.

Part of the work presented previously at Austin Doyle Award Session, ISH 2012, Sydney, Australia. ESH 2013, Milan, Italy.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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## Reviewers' Summary Evaluations

### Reviewer 1

The article supports the hypothesis that hypertension and osteoporosis might share components of accelerated aging.

### Reviewer 2

The article deals with an important, although previously studied, topic. A strong point is the large number of subjects studied. A weak point is the lack of data about previous vertebral fractures (and their possible influence on height) in the studied population.