Extended Abstract

Heterogeneity Identified at Birth and Hypertension Risk at Adulthood

F Fang[1], EK O'Neill[2], G. DiRienzo[3], TB Gage[2,3,*]

[1] Center for Social and Demographic Analysis, University at Albany – SUNY

[2] Department of Anthropology, University at Albany - SUNY

[3] Department of Epidemiology and Biostatistics, University at Albany – SUNY

* Corresponding author.

AS 114, Department of Anthropology, University at Albany – SUNY,
Albany, NY 12222.
Tel: 518-442-4704.
Fax: 518-442-5710.
Email: tgage@albany.edu

ABSTRACT

Birth weight is often used as an indicator of fetal programming and a risk factor of chronic disease later in life. This paper examined the association of birth weight with blood pressure at age 46 by applying Covariate Density Defined mixture of regressions (CDDmr) to the 1958 National Child Development Study. CDDmr identifies two latent subpopulations, interpreted as undergoing "normal" and "compromised" fetal development. Compared to "normal" births, the mean systolic blood pressure of "compromised" births is 20 and 28 mmHg higher among females and males, respectively. The relative risk of stage-I systolic hypertension (>140 mmHg) between the "compromised" and the "normal" subpopulation is 6.9 and 3.4 by sex. The relative risk of stage-II systolic hypertension (>160 mmHg) is even higher, 70.6 and 35.0 by sex. Results for diastolic blood pressure are similar. CDDmr is likely to be useful for studying fetal programming as a complex phenotype.

INTRODUCTION

Hypertension is one of the most important risk factors for cardiovascular diseases and a leading cause of death worldwide. A large body of research has demonstrated that genotype, physical condition (e.g. age and body mass index), socioeconomic status, and adult life style (e.g. excessive food and salt intake, lack of exercises, stress, and smoking) all contribute to hypertension. In addition, many epidemiological studies show that the developmental origin of chronic diseases (including hypertension) begins before birth (Calkins and Devaskar 2011). The "Barker hypothesis" posits that adverse influences during fetal development may be associated with differential organ development, increased allocation of nutrients to adipose tissue, accelerated weight gain in childhood, and a greater risk of diseases later in life.

Birth weight is commonly used as an indicator of fetal programming. Birth weight is often found to be inversely associated with blood pressure in both adulthood and childhood. However, earlier analyses of birth weight and infant mortality have shown that birth cohort is not homogenous (Gage, Bauer et al. 2004; Gage, Fang et al. in press). However, the correlations of birth weight with chronic diseases of aging reported in the literature do not consider this latent heterogeneity. Consequently, they may be biased or even severely biased. In this study, we used a latent mixture method, rather than the conventional regression approach, to re-examine the association of birth weight with diseases of aging, specifically high blood pressure at adulthood.

METHODS

Source of Data

The 1958 longitudinal National Child Development Study (NCDS) includes all infants born in England, Scotland, and Wales during March 3rd-9th, 1958 (Power and Elliott 2006). Follow up of surviving children was conducted at age 7, 11, 16, 20, 23, 33, 42, 45, 46 and 50. A large number of health and medical data were collected. In particular, birth weight of 8143 girls and 8638 boys was recorded (originally in pounds and ounces, and converted to grams in this study). Blood pressures of approximately

50% these participants were measured by trained medical personnel in 2004 (i.e. at age 46). Detailed description of the data used in this project is summarized in Table 1.

Table 1 about here

Statistical Model – CDDmlr

Following Gage (2002), the CDDmlr model includes two steps (or stages). First, the birth weight (x) density is modeled as a mixture of two Gaussian distributions:

$$f_1(x;\theta) = \pi_s \cdot N\left(x;\mu_s,\sigma_s^2\right) + (1-\pi_s)\cdot N\left(x;\mu_p,\sigma_p^2\right) \qquad \text{(Eq. 1)}$$

π_s, the mixing proportion, is defined as the proportion of births belonging to the less numerous of the two subpopulations, that is, the secondary (s) subpopulation as opposed to the primary (p) subpopulation. For i = s and p, $N\left(x;\mu_i,\sigma_i^2\right)$ represents the Gaussian distribution with mean μ_i and variance σ_i^2.

Second, a weighted estimation technique is applied to the regression of blood pressure (y) by birth weight (x). In particular, the blood pressure of the total population at each birth weight is a weighted sum of the blood pressures of the secondary and the primary subpopulations at each particular birth weight:

$$f_2\left(y \mid x;\theta,\beta_s,\beta_p,\varepsilon_s,\varepsilon_p\right) = q_s(x;\theta)\cdot N\left(y;g_s(x;\beta_s),\varepsilon_s^2\right) + (1-q_s(x;\theta))\cdot N\left(y;g_p\left(x;\beta_p\right),\varepsilon_p^2\right) \qquad \text{(Eq. 2)}$$

$q_s(x;\theta)$ is the posterior probability of latent group membership (i.e. the probability of being a secondary birth) given a particular birth weight. The birth weight density submodel (Eq. 1) determines that:

$$q_s(x;\theta) = \frac{\pi_s \cdot N\left(x;\mu_s,\sigma_s^2\right)}{\pi_s \cdot N\left(x;\mu_s,\sigma_s^2\right) + (1-\pi_s)\cdot N\left(x;\mu_p,\sigma_p^2\right)} \qquad \text{(Eq. 3)}$$

For i = s and p, the subpopulation specific blood pressure by birth weight association is modeled by a 2nd-order linear regression:

$$g_i\left(x;\beta_i = \left(\beta_{i,0},\beta_{i,1},\beta_{i,2}\right)\right) = \beta_{i,0} + \beta_{i,1}\cdot x + \beta_{i,2}\cdot x^2 \qquad \text{(Eq. 4)}$$

Model Fitting

The models (Eq. 1 and 2) are fitted sequentially using the method of maximum likelihood to individual level data using ms() in the SPLUS statistical library.

Hierarchical analysis is carried out to determine the significance of parameters in the subpopulation specific blood pressure by birth weight regression.

RESULTS

The birth weight distribution characteristics of 1958 British birth cohort are presented in Figure 1. The secondary subpopulation accounts for 12.7% and 11.8% of the female and males births, respectively. Compared to primary births of the same sex, secondary births have a significantly lower mean birth weight (by 425-500 grams), but a significantly larger standard deviation (by 488-522 grams). Consequently, the primary subpopulation is largely confined to the normal birth weight range and is interpreted as births with "normal" fetal growth. On the other hand, the secondary subpopulation accounts for most births in both the lower and upper tails of the birth weight distribution as well as some births in the normal birth weight range. Hence, it is interpreted as "compromised" births (i.e. they have experienced an adverse environmental stimulus during fetal development). This interpretation of the latent subpopulations is similar to that used in Gage's studies of infant mortality (Gage, Bauer et al. 2004; Gage, Fang et al. in press).

Figure 1 about here

Overall, eight nested models illustrating various blood pressure by birth weight correlations were fitted to the data (Eq. 2). A standard chi-square test (d.f. = 3, p-value $<< 10^{-3}$) shows that there is significant heterogeneity in the association of blood pressure (both systolic and diastolic) at age 46 with birth weight between "compromised" and "normal" births in both sexes (Table 2). Blood pressure of "normal" females appears to be a negative linear function of birth weight, while the full model (Eq. 4) is the most parsimonious model in males (Table 2). Therefore, sex specific models are used in all analyses.

Table 2 about here

The CDDmr-predicted blood pressure by birth weight curves are illustrated in Figure 2. Both systolic and diastolic blood pressures are more sensitive to birth weight

change among "compromised" births compared to "normal" births. Also, adult blood pressure of "compromised" births is generally higher than that of "normal" birth in the range of 2000-5000 grams. Overall there is a weak and negative correlation of blood pressure with birth weight in both sexes as commonly observed (Law and Shiell 1996; Mu, Wang et al. 2012). Furthermore, the model-predicted blood pressure by birth weight relationship for the total cohort is slightly U-shaped, although neither of the subpopulations is U-shaped (Fig. 2). The U- shape is due to two characteristics of "compromised" births: i) consistently higher blood pressure across birth weight, and ii) higher frequencies at both ends of the birth weight spectrum (Fig. 1). Therefore, CDDmr analysis confirms an increased risk of hypertension for people with low birth weight, and possibly high birth weight as well, at the population level.

Figure 2 about here

The CDDmr-predicted mean diastolic blood pressure of "compromised" births is higher by 12 and 16 mmHg in females and males, respectively (Table 3, Figure 3). Also the mean systolic blood pressure is higher by 20 and 28 mmHg in females and males, respectively. Therefore, about 40% of all participants with stage-I hypertension (i.e. > 90 mmHg for diastolic and > 140 mmHg for systolic) at age 46 are composed of "compromised" births, which suffer from a stressed fetal growth (Table 4). In addition, approximately 80% of all participants with stage-II hypertension (i.e. > 100 mmHg for diastolic and > 160 mmHg for systolic) are accounted for by the "compromised" subpopulation. Therefore, compared to "normal" births, the relative risk of developing stage-I hypertension is at least tripled for "compromised" births and almost 18 times higher for stage-II hypertension.

Table 3 about here

Figure 3 about here

Table 4 about here

Analysis with CDDmr also clearly demonstrates a sex difference in blood pressure at adulthood and in the fetal programming of hypertension as observed in other studies (Gilbert and Nijland 2008; Grigore, Ojeda et al. 2008). In particular,

CDDmr predicts a somewhat larger effect of birth weight on blood pressure in males than in females among the "compromised" subpopulation. Moreover, there is likely to be a sex specific response of blood pressure with respect to the change in birth weight among births with "normal" fetal growth as well. In particular, CDDmr estimates that a 1-kg increase in birth weight is associated with an approximately 2-mmHg decrease in systolic (as well as diastolic) blood pressure among females with "normal" fetal growth (Figure 2). However, for males with "normal" fetal development, the same change in birth weight might not be beneficial with respect to blood pressure. Therefore, blood pressure (both diastolic and systolic) is higher in males than females (Figure 2) and males have a greater risk of developing hypertension among both "normal" and "compromised" subpopulations (Table 4). However, the relative risk of adult hypertension between "compromised" vs. "normal" male births is approximately half of the value among female births.

DISCUSSION

A major limitation of using the 1958 NCDS data (as well as any longitudinal study) is the potential bias due to the unavoidable losses through death and/or emigration as well as avoidable sample attrition (e.g. failure in follow up and refusal to participate further) (Atherton, Fuller et al. 2008). From the beginning of the study until 2004, almost 50% of the initial participants are lost. The loss of births with extreme birth weights seems to occur more frequently than births with birth weight in the normal range. The loss of these "compromised" births is likely due to death during infancy. On the other hand, members of the "compromised" subpopulation, if they survive infancy, are most likely to be associated with adverse medical/health outcomes in childhood and adulthood due to fetal programming. Therefore, the "compromised" subpopulation appears to be underrepresented and the statistical power on "compromised" births may be reduced. We are currently developing an advanced algorithm (i.e. AIPWCC, the augmented inverse probability weighted complete case) which should resolve this issue by modeling selection bias due to death as well as non-random loss in follow-ups.

Some researchers have argued that birth weight is of little relevance to blood pressure levels in later life (Law and Shiell 1996; Huxley, Neil et al. 2002). The inverse association between birth weight and subsequent blood pressure may disappear after adjusting for confounding factors such as current age, weight, and BMI. Applications of CDDmr to birth outcomes (Gage, Fang et al. 2009; Gage, Fang et al. 2010; Gage, Fang et al. in press) and childhood obesity (unpublished results) have demonstrated that CDDmr can be easily modified to test this hypothesis by incorporating potential confounding factors into the model as exogenous covariates. Nevertheless, caution must be taken if a statistical adjustment is to be made. Because inappropriate controlling of alleged confounders, which ultimately are not confounders but colliders on the causal pathway, can generate unexpected bias and create an artifactual statistical effect known as the "reversal paradox" (Tu, West et al. 2005).

In this analysis, the association between birth weight and diastolic blood pressure is as strong as the association of birth weight with systolic blood pressure. However, many studies in the literature conclude that this association primarily exists between birth weight and systolic blood pressure (Fagerudd, Forsblom et al. 2004; Mu, Wang et al. 2012). It is possible that the hidden heterogeneity in birth cohort has masked the correlation of diastolic blood pressure with birth weight. By controlling for this heterogeneity, CDDmr portraits a better picture of the fetal programming of hypertension.

Earlier CDDmr analysis of birth outcomes indicated that "normal" and "compromised" are heterogeneous with respect to infant mortality. In particular, "compromised" births have lower birth weight specific mortality compared to their "normal" peers, but a higher overall mortality. For "compromised" births that survive childhood, despite generally being smaller at birth, they have faster growth rate. So that, by age 7, their BMIs exceed those of their birth weight specific peers in the "normal" subpopulation and accounts for most the overweight and almost all of the obese children in the birth cohort. Furthermore, CDDmr analysis demonstrates that at age 45, surviving "compromised" births are more likely to develop hypertension than

"normal" births. Therefore, CDDmr identifies births with accelerated post-birth growth rates without the need for early growth data, resolves the birth weight BMI paradox described in the fetal programing literature, and supports the fetal programming hypothesis of hypertension. It may prove d to be a very useful statistical method to determine if the "compromised" subpopulation, if survive child/adulthood, also accounts for most cases of metabolic syndrome, type II diabetes and heart disease and fetal- programmed births in general.

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Table 1 Statistical description of birth weight (gram) and blood pressure (mmHg) at age 46# for members of the 1958 British birth cohort

	Females			Males		
	Birth Weight	Diastolic BP	Systolic BP	Birth Weight	Diastolic BP	Systolic BP
sample size	8143	4275	4276	8638	4230	4230
minimum	369	35	72	312	42	88
5th percentile	2298	60	97	2384	66	111
25th percentile	2923	69	110	3036	75	123
50th percentile	3235	76	120	3405	82	133
75th percentile	3604	83	132	3746	90	144
95th percentile	4086	95	150	4256	102	163
maxium	6016	147	234	5732	145	213
mean	3228	76	122	3365	83	134
stdev	567	11	17	584	11	16
skewness	-0.6	0.5	0.6	-0.6	0.5	0.8
kurtosis	2.2	1.2	1.1	1.9	0.6	1.3

#: members with birth weight information available as well

Table 2 Nested Chi-Sq. tests

Stage-2 Parameters	Diastolic BP		Systolic BP	
	Females	Males	Females	Males
$\beta_{s,0}$, $\beta_{s,1}$, $\beta_{s,2}$, $\beta_{p,0}$, $\beta_{p,1}$, $\beta_{p,2}$	16274.7	16067.2 *	18025.1	17637.1 *
$\beta_{s,0}$, $\beta_{s,1}$, $\beta_{s,2}$, $\beta_{p,0}$, $\beta_{p,1}$	16276.0 *	16071.1	18025.2 *	17641.0
$\beta_{s,0}$, $\beta_{s,1}$, $\beta_{p,0}$, $\beta_{p,1}$, $\beta_{p,2}$	16282.5	16086.3	18039.3	17664.6
$\beta_{s,0}=\beta_{p,0}$, $\beta_{s,1}=\beta_{p,1}$, $\beta_{s,2}=\beta_{p,2}$	16332.9	16124.5	18097.7	17808.7

*: the most parsimonious model at α=0.05 level

Table 3 CDDmr-predicted mean blood pressure (mmHg) at age 46

	Females		Males	
	Diastolic	Systolic	Diastolic	Systolic
"Compromised"	87	139	97	159
"Normal"	75	119	81	132
Total	76	122	83	134

Table 4 Decomposition analysis of CDDmr-predicted hypertension rate at age 46 and relative risk of hypertension between "compromised" vs. "normal" births

	Females				Males			
	Composition (%)			Relative Risk	Composition (%)			Relative Risk
	"Compromised"	"Normal"	Total		"Compromised"	"Normal"	Total	
Diastolic Hypertension								
Stage-I *	5.3	5.9	11.2	7.1	8.1	16.7	24.7	4.4
	(47)	(53)	(100)		(33)	(67)	(100)	
Stage-II **	2.4	0.5	2.9	35.0	4.9	2.4	7.3	19.3
	(81)	(19)	(100)		(68)	(32)	(100)	
Systolic Hypertension								
Stage-I &	6.1	7.1	13.2	6.9	9.0	24.5	34.3	3.4
	(46)	(54)	(100)		(27)	(73)	(100)	
Stage-I &&	2.2	0.2	2.4	70.6	5.9	1.6	7.5	35.0
	(90)	(10)	(100)		(79)	(21)	(100)	

*: above 90 mmHg **: above 100 mmHg

&: above 140 mmHg &&: above 160 mmHg

Figure 1 Model-predicted birth weight distributions: Females of the 1958 British birth cohort. Results for males are similar.

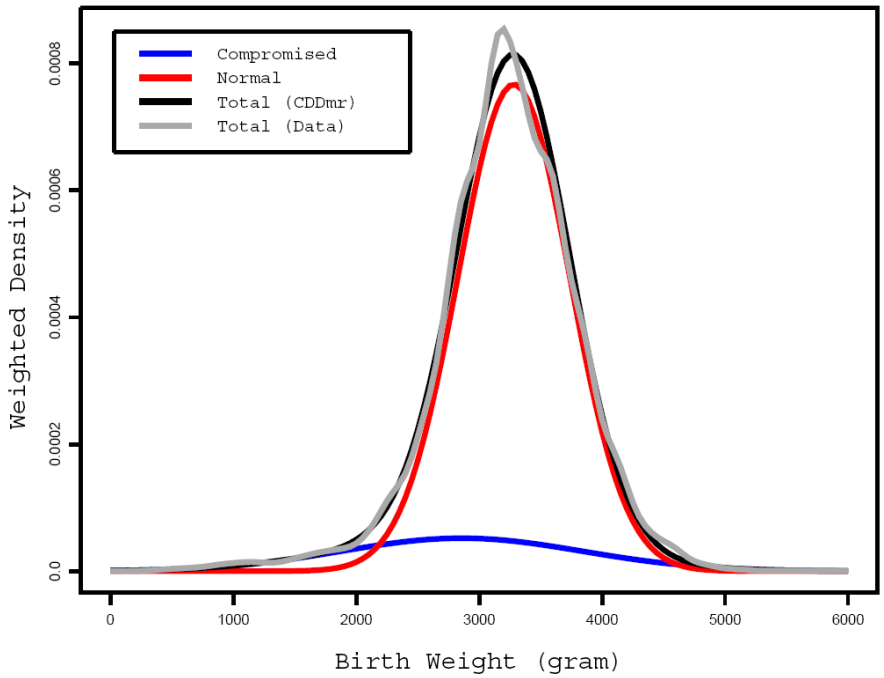
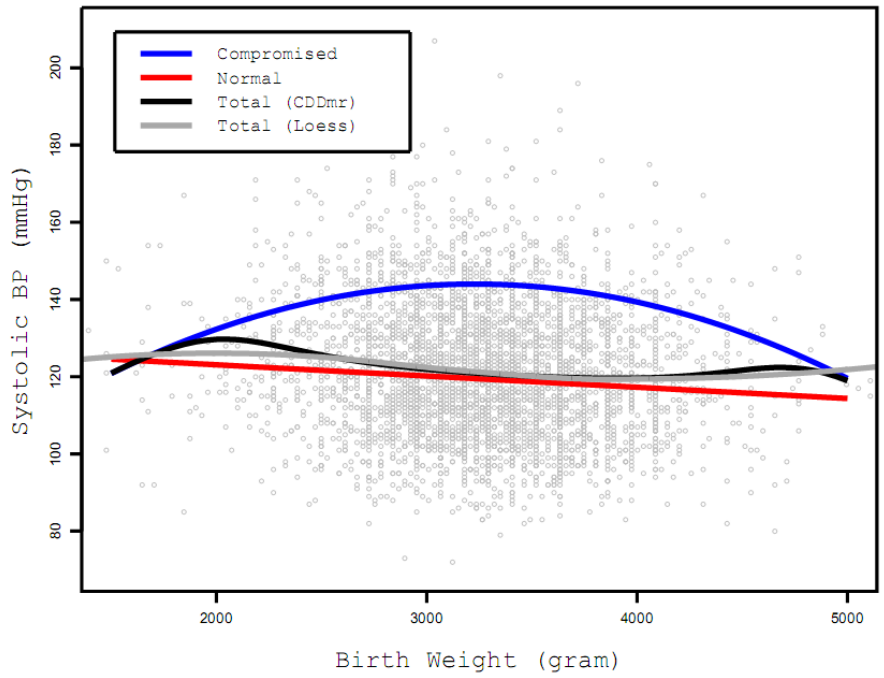


Figure 2 Model-predicted systolic blood pressure by birth weight curves at age 45: (a) Females and (b) Males of the 1958 British birth cohort. Results for diastolic blood pressure are similar.

(a) Females



(b) Males

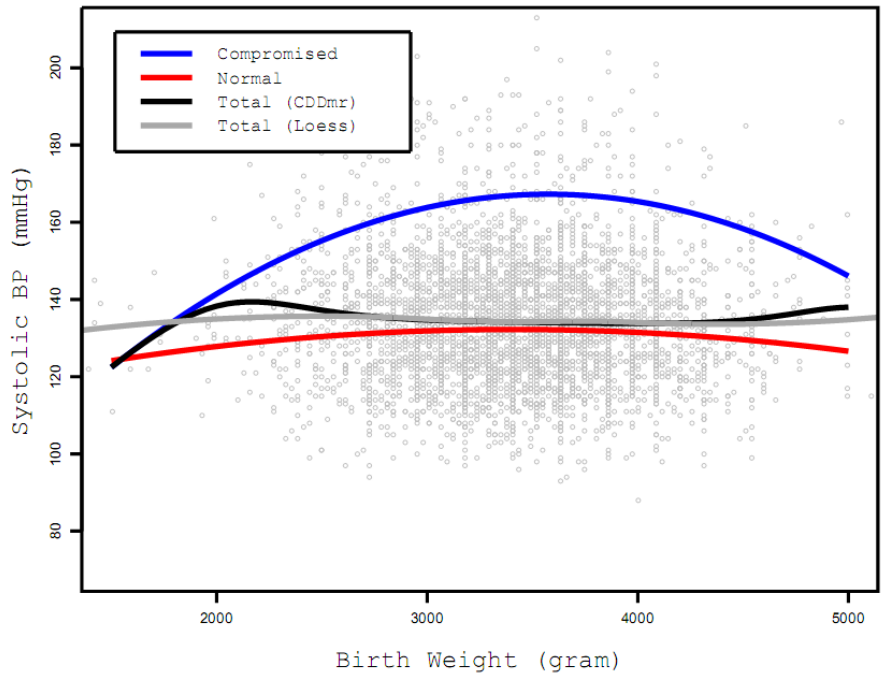
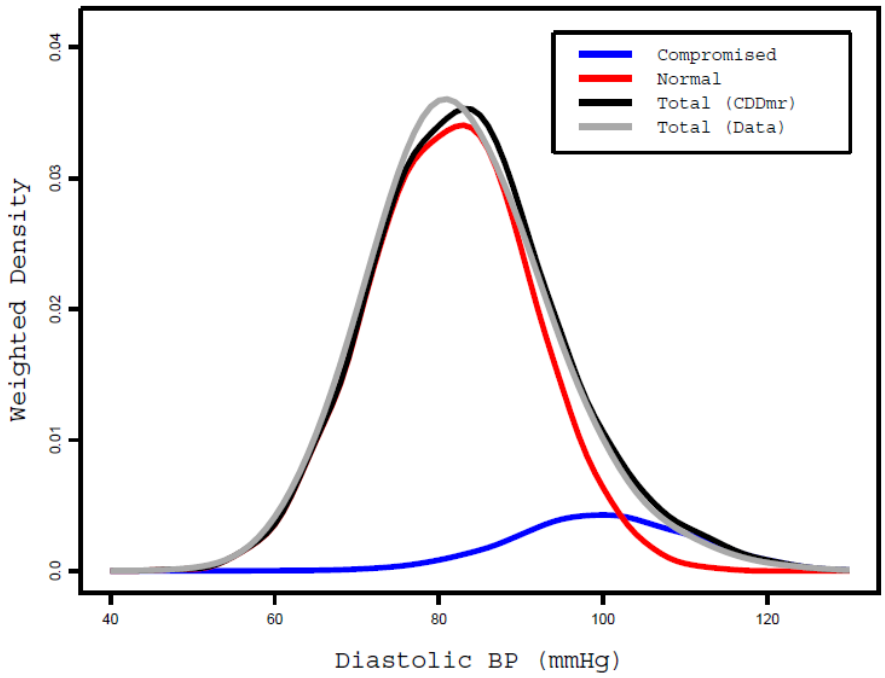


Figure 3 Model-predicted blood pressure distributions at age 45: Males of the 1958 British birth cohort. Results for females are similar.

(a) Diastolic BP



(b) Systolic BP