AGE AT MENARCHE AND MENOPAUSE: THEIR CORRELATES AND ASSOCIATION WITH SELECTED CARDIOVASCULAR DISEASE RISK FACTORS AMONG 300 000 CHINESE WOMEN IN THE CHINA KADOORIE BIOBANK

by

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Abstract

Age at menarche and menopause: their correlates and association with selected cardiovascular disease risk factors among 300 000 Chinese women in the China Kadoorie Biobank

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Background: Age-standardised mortality rates for cardiovascular disease (CVD) are generally higher among men than women, prompting suggestions that reproductive factors may be partly responsible. Moreover, there have been major changes in women's reproductive patterns and CVD rates in China over the last few decades, but the association between them is still poorly understood.

Objectives: To start addressing these issues, this thesis examines the secular trends and correlates of age at menarche and menopause (the major physiological events defining a woman's reproductive window), as well as their association with blood pressure and anthropometry in 302 180 women born in 1930-74 from 10 areas across China using cross-sectional demographic, behavioural, physical and reproductive data from the China Kadoorie Biobank.

Results: Mean age at menarche decreased by 2 years over a 44-year period (1930-1974), with the exception of an increase of about 1 year for women exposed to the Great Chinese Famine in early adolescence. No other factor showed as large an effect on age at menarche. Among women aged ≥57 years at the baseline, mean age at menopause increased by 1.4 years over a 21-year period (1930-1951) and was significantly associated with several reproductive and behavioural factors, notably gravidity (2 years later menopause) and smoking (6 months earlier menopause). Blood pressure and anthropometry were weakly inversely associated with age at menarche (0.2mmHg and 0.2kg/m^2 lower per year later menarche) and even more weakly positively associated with age at menopause (0.06mmHg and 0.04kg/m^2 higher per year later menopause). These trends and associations all varied to some extent by area and socioeconomic status. (All p-values <0.0001)

Conclusion: This study adds new information on the secular trends and correlates of age at menarche and menopause in a large Chinese population born around the mid-20th century and provides a basis for further prospective work on the association of reproductive history with the incidence of CVD in China.

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Contents

List of abbreviations

95% CI	95% confidence interval
BFP	Body fat percentage
BMI	Body mass index
CKB	China Kadoorie Biobank
CTSU	Clinical Trials Services Unit and Epidemiological Studies Unit
CVD	Cardiovascular disease
DALYS	Disability-adjusted life-years
DBP	Diastolic blood pressure
GnRH	Gonadotrophin-releasing hormone
GWA	Genome-wide associations studies
HC	Hip circumference
HRT	Hormone replacement therapy
ICC	Intra-class correlation coefficient
IHD	Ischaemic heart disease
MRC	Medical Research Council
NCD	Non-communicable chronic disease
OC	Oral contraceptives
RCT	Randomised controlled trials
RMB	Renminbi
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SES	Socioeconomic status
USA	United States of America
WC	Waist circumference
WHR	Waist-hip ratio
WWII	World War II

Chapter 1. Introduction

This thesis examines the secular trends, regional variations and correlates of age at menarche and menopause as well as their relationship with selected cardiovascular disease (CVD) risk factors among Chinese women born in the mid-20th century.

1.1 Rationale for examining reproductive trends and their association with CVD

Sex-related differences in CVD have been noted in both developed and developing countries. At the end of the last century, the age-standardised mortality rates for both ischaemic heart disease (IHD) and stroke were higher among men than women in most regions of China [1] and in the UK (Figure 1). Evidence from Western populations suggests that this difference is most marked below age 50 [2], when premenopausal women appear to be relatively protected against cardiovascular events such as IHD compared to age-matched men. After menopause, female rates seem to rise rapidly to become comparable to those of men [3-5]. This pattern suggests that greater exposure to oestrogen may alter risk profile, leading to reduced risk of CVD in premenopausal women compared to age-matched men and to postmenopausal women. However, to date, controversy remains over the effect of oestrogen exposure – which is determined by a woman's reproductive history – on CVD, especially among postmenopausal women.

China has seen major socioeconomic and political reform in the 20th century. Among other significant consequences, this has resulted in substantial changes in reproductive patterns among Chinese women [6] as well as a rapid epidemiological transition in recent decades, with a shift from a burden of predominantly infectious diseases to predominantly non-communicable chronic diseases (NCDs) [7]. However, despite this generally increasing burden of NCDs throughout China, there are up to 5-fold variations in the mortality rates of many common NCDs such as CVD across different areas and between sexes for reasons that are still poorly understood [8]. The aim of this thesis, therefore, is to examine changes in, and correlates of, age at menarche and menopause (which determine the window of endogenous oestrogen exposure) and their associations with known CVD risk factors in an attempt to understand the role female hormones may play in the risk of CVD.

1.2 Reproductive changes in China over the 20th century

China has undergone the fastest fertility transition in the world [9] beginning around 1971-73 [10], due primarily to the implementation of the One Child Policy in China rather than any spontaneous societal change towards smaller families. Throughout the 20th century there has been a falling fertility rate [9-21] due to a rising age at first marriage [9-11, 14, 19] despite a higher marriage rate among young people [14, 15], increasing interval between consecutive births [14, 18], and increasing use of contraception [9, 10, 21] (including more permanent forms such as tubal ligation [22]). A decrease in the interval between marriage and first birth [10, 16, 19] together with an increase in premarital conceptions [19] do not appear to have significantly delayed this fall in fertility. Breastfeeding also became more widespread, possibly because of increased recognition of the role of breastfeeding in child survival and birth spacing [17]. These secular changes were seen across all areas of China [6, 20] although differences between areas persist [9, 16] due in large part to differential enforcement of [9, 18] and continuing resistance to the

One Child Policy [9, 16]. For example, while age at marriage became comparable between urban and rural women, the rural fertility rate was twice that seen in urban areas from 1966 to 1990 [23] with central Chinese states such as Hunan, Gansu and Henan having some of the highest fertility rates [20].

However, political factors are not likely to account substantially for any secular trends and regional differences in age at menarche and age at menopause in China. Several important correlates of age at menarche [24-39] and menopause [40-49] are known, but the data are derived largely from studies in western populations. Limited evidence from Chinese populations (see Literature Review), however, suggests that the dramatic improvements in the socioeconomic and nutritional status of the Chinese population over the 20th century are likely to have impacted on age at menarche and – together with the above reproductive trends – age at menopause (see Literature Review). Further examination of the secular trends and correlates of these reproductive factors in China is warranted given the major environmental and reproductive changes experienced by Chinese women.

1.3 The epidemiological transition in China in the 20th century

As part of the epidemiological transition in 20th century China, the prevalence of risk factors for NCDs such as obesity and hypertension increased [50] but remains lower than in many developed countries [51]. The 2002 National Nutrition and Health Survey reported that 184 million Chinese (15%) were overweight and a further 31 million (3%) were obese [52]. These numbers may in fact underestimate the burden of obesity in China, as conventional definitions of body mass index (BMI) ($\geq$25kg/m^2 for overweight and $\geq$30 kg/m^2 for obesity) were used, whereas definitions of lower BMIs of 24.0-27.9 kg/m^2 for overweight and ≥28 kg/m^2 for obesity have been recommended for China [53, 54]. Similarly, the International Collaborative Study of Cardiovascular Disease in ASIA (InterASIA) found that over a quarter of Chinese adults aged 35-74 years in 2000-01 had hypertension [55]. Prevalence of hypertension increased with age but was consistently higher in men than women, and more than half the participants were unaware of their hypertension prior to enrolment in the study [55]. Furthermore, while regional differences persist, the prevalence of hypertension in rural areas is rapidly approaching that of urban areas [56]. As a result of the increase in the prevalence of risk factors, NCDs are currently responsible for approximately 80% of deaths and 69% of disability-adjusted life-years (DALYs) lost among the adult Chinese population (Figure 2) [7, 57].

1.4 Current evidence on the association between reproductive factors and CVD risk factors

The majority of the limited literature on reproductive patterns and their association with CVD comes from studies in North America and Europe where disease rates differ significantly from that of a Chinese population. Most research on this association has looked at the effect of exogenous oestrogen – most commonly administered as either an oral contraceptive (OC) or hormone replacement therapy (HRT) – on CVD. There is good evidence from observational studies that low-dose OC use is associated with increased risk of myocardial infarction and stroke [58] (Appendix A). However, the protective effect of HRT reported in observational studies was not confirmed in randomised controlled trials (RCTs), reflecting chiefly residual confounding in the former: women who chose to take HRT – rather than being assigned to it in RCTs – generally had higher socioeconomic status [59], better risk profiles [60] as well as better compliance adding to a healthy cohort effect [61] (Appendix A).

Endogenous oestrogen – the other major type of exposure – refers to sex hormones produced by a woman's ovaries in her reproductive lifetime and the period of exposure is bracketed by menarche and menopause. All other reproductive events occurring during this period, as well as factors affecting timing of menarche and menopause, can also affect endogenous oestrogen exposure. Despite the same starting point, investigation into the effects of exogenous and endogenous oestrogens on CVD has evolved in parallel. Limited work has been done to examine the effect of reproductive factors that determine endogenous oestrogen on CVD and most studies have focused on age at menopause as a predictor for CVD post-menopause [62]: a 2006 meta-analysis of 12 studies from 1966-2004 found a pooled relative risk of 1.38 (95%CI 1.21-1.58, adjusted for current age and smoking) [62], which was supported by two prospective studies conducted in 37 965 Japanese [63] and 2658 Korean women [64]. However, uncertainty persists about the effects of menopause status on CVD risk and there is still very limited evidence that other reproductive factors (e.g. age at menarche and parity) are associated with CVD [65]. Furthermore, information on the association of reproductive history with known CVD risk factors such as blood pressure and anthropometry is inadequate, inconsistent and derived primarily from small studies in Western populations (see Literature Review). Despite these limitations, current evidence suggests a protective effect of later age at menopause [62] and longer duration between age at menarche and age at menopause [62, 66] (Appendix A).

1.5 Contribution of this thesis

Partly as a result of the major changes in reproductive behaviour among Chinese women, rates of reproductive organ diseases such as breast cancer also show secular trends and regional variations [67]. More evidence on the association between reproductive history and CVD risk factors, as the intermediate step, may clarify whether these large changes in female reproductive history would have a similar effect on CVD rates among postmenopausal women in China. This question cannot be addressed comprehensively within the scope of this thesis. Instead, using data from 300 000 women in the China Kadoorie Biobank, this study assesses firstly secular trends and known correlates of age at menarche and menopause – determined predominantly from studies in Western populations – to establish what changes have taken place and what correlates may be relevant in a Chinese population. Secondly, this study contains preliminary analyses on any associations between these major reproductive factors and blood pressure and anthropometry as two known CVD risk factors. This thesis therefore serves as a starting point to later work by the China Kadoorie Biobank in addressing more thoroughly the question of what impact reproductive factors may have on CVD among Chinese women. Although any effect of reproductive history on CVD will be modest by comparison to other known CVD risk factors such as smoking, the relevance of reproductive factors – as surrogate measures of exposure to endogenous sex hormones – to women's health continues to be of public health significance. Large prospective cohort studies, despite their inherent limitations when compared with RCTs, could provide reliable assessment of the effects of a wide range of reproductive factors on health, provided proper attention is paid to random error, confounding factors and biases when analysing and interpreting study findings.

Figure 1. Geographic variations of age-standardized mortality rates for ischaemic heart disease and stroke in rural China, aged 35–69 (per 100 000), 1986–88. Each letter in the figure represents one county. Comparable rates for UK males and females for 1990 are also shown [8]

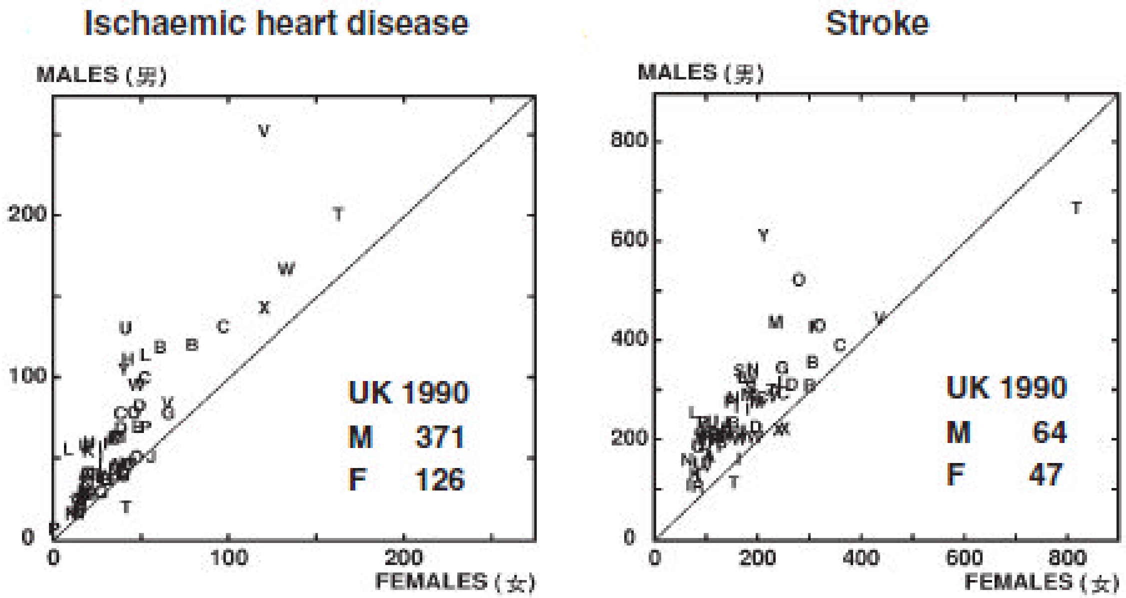
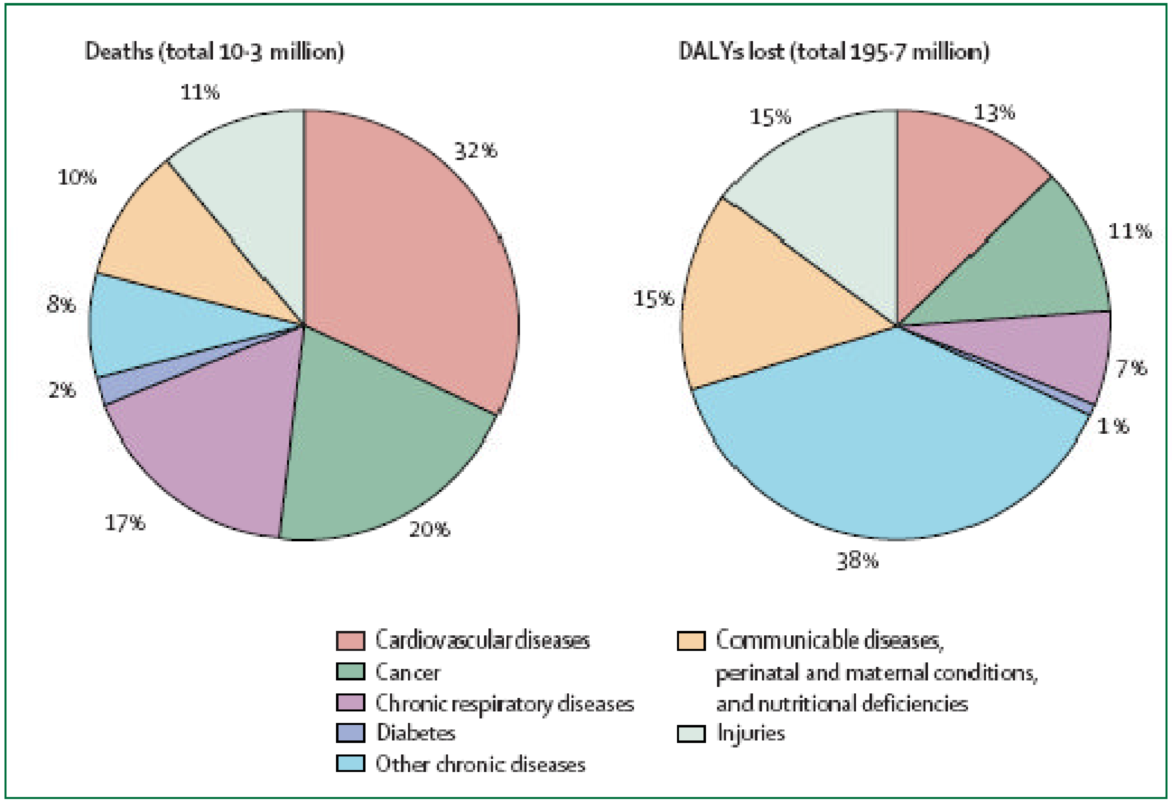


Figure 2. Estimated proportion of total deaths and DALYs lost for all ages in China (Western Pacific Regional Office of World Health Organisation, 2005)[7]



Chapter 2. Literature Review

2.1 Introduction

This thesis contains a selective critical review of previous studies on the secular trends and correlates of age at menarche and age at menopause, as well as the association of age at menarche and menopause with certain CVD risk factors. For age at menarche, the main factors of interest were famine exposure (as a measure of acute nutritional insults in childhood), adult height (as a proxy for overall childhood nutritional status), socioeconomic factors and month or season of birth. For age at menopause, the main factors of interest were reproductive history, behavioural factors (specifically soy consumption, smoking and alcohol use), socioeconomic factors and BMI in early adulthood. For the association of age at menarche and menopause with CVD risk factors, the review focused on blood pressure and anthropometry.

This is not intended to be a comprehensive review of all literature on any of the above 3 topics, but aims to cover sufficient background to contextualise the work done in this thesis. Using the Sciverse Scopus database search engine, studies were selected for inclusion according to the following criteria:

1. Original research articles (no reviews) published 1970-2010 with full text in English
2. Study population ≥500 (or number of naturally menopausal women ≥500)
3. Study design involved cross-sectional or longitudinal cohorts only
4. Use of same outcomes and exposures as those examined in this thesis
5. Limited to health sciences subject field and participants not selected to examine the impact of a specific disease e.g. Turner's Syndrome on age at menarche

Overall, a total of 79 studies were selected, including 32 for age at menarche, 29 for age at menopause and 18 for reproductive history and CVD risk factors. The reviews on age at menarche and menopause also include a brief overview of relevant physiology and population trends before summarising the existing evidence on selected known correlates of age at menarche and menopause. Further details on each study included in this review are provided in Tables 1-3 at the end of the chapter. Each section of this chapter contains a summary of the available evidence where the strengths and limitations of the included studies are noted and the gaps in current knowledge highlighted.

2.2 Age at menarche

Specific research into determinants or correlates of age at menarche has been conducted since at least the 1970s. Although these studies have identified a number of factors that could potentially affect age at menarche, in particular those related to childhood exposures, there is little consensus on the mechanisms by which they act. Furthermore, most of the available evidence is derived from cross-sectional or small prospective studies of North American and European populations. There is limited information from developing countries (such as China), some of which have undergone a rapid change in women's reproductive patterns.

Of the 32 articles on secular trends and correlates of age at menarche included in this review, 30 were cross-sectional, 1 a retrospective cohort and 1 a prospective cohort. Sample sizes ranged from 516 to 286 205 women, with the majority of studies conducted in European populations, although a few studies were conducted in African, Asian and South American populations (see Table 1. Literature Review: Correlates of age at menarche).

2.2.1 Menarche: physiology, timing and the role of genes

Puberty is a developmental phase characterised by the appearance of secondary sexual characteristics, the adolescent growth spurt and the attainment of fertility manifested in menarche. It results from the re-activation of the hypothalamo-pituitary-gonadal axis, which is dormant after the first 6 months of life [68]. Sexual maturation is initiated with the pulsatile nocturnal secretion of gonadotrophin-releasing hormone (GnRH) by hypothalamic neurones. GnRH stimulates the anterior pituitary to release luteinising hormone and follicle-stimulating hormone which cause ovarian growth and secretion of sex hormones including oestrogen. Sustained oestrogen secretion produces growth and development of the female reproductive tract in a predictable sequence. Menarche, the first instance of menses, usually occurs approximately 2 years after onset of breast development [69], and results from the gradual thickening of the endometrium induced by rising but fluctuating oestrogen levels.

Under normal circumstances, there is a 4–5 year variation in the timing of puberty among healthy individuals in any given population, which probably reflects differences in environmental factors and genetic variation between individuals [70-73]. In rare situations, there can be precocious puberty (i.e. signs of sexual maturation ≤8 years), which is more commonly reported in females [69] and is generally due to premature activation of the hypothalamo-pituitary-gonadal axis (e.g. by a neoplasm). Rarely, there can be pathological pubertal delay (i.e. primary amenorrhoea[1]), which is most commonly associated with chronic illness, stress and under-nutrition.

Recently, family and twin studies have shown maternal age at menarche as a strong predictor of age at menarche in the next generation [33, 35, 38]. Population-based genome-wide association studies (GWAS) have identified several loci that are strongly associated with age at menarche, notably the FTO and TMEM18 genes (which are the two loci with the largest observed effects on BMI) [35] and 6q21 (which overlaps with the LIN28B gene involved in normal height variation) [33, 35]. Different haplotypes within

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[1] Primary amenorrhoea is defined either as absence of menses by age 14 years with the absence of growth or development of secondary sexual characteristics (e.g. breast development) or as absence of menses by age 16 years with normal development of secondary sexual characteristics.

the block containing the relevant single nucleotide polymorphisms on 6q21 have been associated with 0.9-1.9 months delay in age at menarche [38]. Further investigation into the LIN28B and FTO genes may clarify the relationship of onset of puberty with height and weight, as well as its possible associations with CVD risk factors. However, the effect of genetic variations on age at menarche is small compared to other significant environmental exposures such as famine.

2.2.2 Secular trends

In both developed and developing countries, there has been a gradual decline in mean age at menarche during the 20th century. In many European countries, mean age at menarche has decreased from 16-17 years in the mid-19th century [73] by 0.1-0.6 years per decade [34, 74-78]. Similar findings have also been reported in the USA, with the mean age at menarche decreasing by 0.3 years per decade in one study of 8822 white American women born in the first half of the 20th century [79]. Although a further sudden fall in age at menarche was reported in the USA in the late 1990s [80, 81], several studies in European countries have shown stagnation of the secular trend after the 1960s [74, 82-84].

Limited data from South American and African countries also showed a decreasing secular trend in the second half of the 20th century. Age at menarche decreased at 0.1-0.5 years per decade in 1955 Brazilian women [85], 3206 Columbian women [25] and 688 Chilean women [86], with no difference in the trend between indigenous and non-indigenous women in Chile [86]. An even greater decreasing secular trend of 0.7 years per decade has been found in a small study of 924 Gambian girls aged 9-20 [87]. In most East Asian countries, there was a decreasing secular trend, although the reported magnitude of the change varied greatly, ranging from 0.2 years per decade among 6467 Chinese girls in Hong Kong born 1974-87 [88] to 0.7 years per decade in 2 studies of more than 1000 South Korean women born 1920-86 [89, 90]. By contrast, a small study of 995 Bangladeshi women born 1979-86 reported a significant increase in age at menarche of 0.1 years per decade [91]. These different secular trends may reflect heterogeneity in socioeconomic status (SES) and development, family size and nutrition within and between countries [73].

Currently, mean age at menarche appears to have stabilised around 13 years for many Asian, South American and European populations [74, 85, 88, 89, 91-93]. It has been suggested that this age is biologically optimal as the population reaches the genetic limits for age at menarche and that the later ages at menarche seen in previous decades may reflect inadequate nutrition as a result of population growth following increased agricultural settlement [71].

2.2.3 Correlates of age at menarche

2.2.3.1 Nutritional factors

While there is consensus that age at menarche is affected by nutritional factors, uncertainty remains about the mechanism of action, the stage of development when sensitivity to nutritional influences is greatest and the effect of acute versus chronic changes in nutritional status.

The effect of nutritional factors differs depending on whether exposure occurs pre- or postnatally. Barker has postulated that a developing foetus may adjust its developmental trajectory to produce a ‘thrifty phenotype’ if exposed to inadequate prenatal nutrition, which assumes that there will be further deprivation after birth [94]. If there is adequate postnatal nutrition, this incorrectly-projected trajectory may produce metabolic features that lead to disease later in life [71]. When prenatal deprivation is followed by a period of childhood nutritional excess, an advance in the age at menarche is usually seen, as in children who have migrated from developing to developed countries [70, 95]. Thus the timing of menarche, which is potentially linked to the ‘thrifty phenotype’ via its association with childhood weight, may indicate maladaptive metabolic homeostasis as a result of competing effects of pre- and postnatal nutrition. On the other hand, assuming adequate prenatal nutrition, a period of postnatal starvation at the time of sexual maturation can delay the attainment of reproductive capacity until the woman is able to cope with the high energy costs incurred by pregnancy and lactation. It has been suggested that postnatal rather than prenatal nutrition may be more important for the timing of puberty [71].

There are questions as to whether an acute versus sustained nutritional insult – either pre- or postnatal – can have a greater effect on menarche. Both chronic under-nutrition and rapid weight loss in adult women can cause changes in and even cessation of menstrual cycles in severe cases [96] and effects on age at menarche may also be seen [68]. Famine exposure represents an acute nutritional insult whereas adult height partly reflects the overall cumulative effect of nutritional status throughout childhood, although it is predominantly determined by genetic factors [97]. Thus both famine exposure and adult height may be associated with changes in age at menarche.

Famine exposure

During the 20th century, various populations have been exposed to famine either as the result of civil conflict or natural disasters. Consequently, several observational studies have specifically examined the effect of pre- and postnatal famine exposure on age at menarche in those countries affected by famine following World War II (WWII), with most evidence coming from studies of the Dutch population. These studies have shown that famine exposure during late childhood and early adolescence is associated with a significant delay of up to a year in mean age at menarche at the population level whereas no such relationship was apparent for prenatal famine exposure.

In many countries affected by WWII, anomalous periods of stagnation or temporary increase in an otherwise decreasing secular trend in age at menarche have coincided with the post-WWII famine or food restrictions. The Netherlands, Germany and France (in increasing order of severity) [34] as well as Japan [98], showed an anomalous period of increase in age at menarche for women born in 1920-34 who were exposed to either famine or food restriction in late childhood or early adolescence. Rural Chuvashian[2] women born in the 1930s – who experienced a pre-adolescent period of food-rationing in 1941-47 – had menarche 0.9 years later than women born in the 1910s [93]. A period of stagnation in the secular trend was noted for 1061 Korean women born in 1930-40 who experienced WWII and the 1950-53 Korean War during their childhood or adolescence [90]. However, it is difficult to separate the effect of general deprivation and increased mental and physical stress from that of famine alone, as seen in approximately 2500 Croatian girls who lived through the 1991-95 civil war where more severe degrees of personal loss were associated with greater delays in age at menarche [99].

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[2] The Chuvash Republic located in the European part of Russia is one of the most densely populated regions in the Russian Federation with an estimated total population of 1.35 million people.

Several studies have noted that these deviations in the secular trend appear to be restricted to those women exposed to famine in late childhood or early adolescence. For example, a closer examination of 653 native Chuvashian women aged 18-90 showed that only women whose "expected" age at menarche (i.e. 15 years) was during the 1941-47 period of food rationing in the Soviet Union experienced an increase in mean age at menarche: 16.7 years for women born in 1925-36 versus 16.0 years for women born in 1937-48 (p=0.005) [100]. Similarly, longitudinal analyses of 21 067 Dutch women born in 1911-1945 showed a temporary increase only for those women whose predicted year of menarche (year of birth +14 years) fell during or immediately after WWII [78].

There is limited information on the association between severity of famine exposure and age at menarche apart from the well-documented events of the 1944-45 Dutch Famine. A cross-sectional study of 21 067 Dutch women born in 1911-1945 who were resident in Utrecht during the famine found no significant association between geographical classification of severity of famine exposure and odds of experiencing menarche, although self-reported severity of famine exposure for the same period was associated with lower odds of experiencing menarche in that year (OR=0.46, 95%CI 0.26-0.83) [78]. However, the former may be confounded by lack of adjustment for SES, and the latter by misclassification bias due to use of self-reporting. Better measures of severity of famine exposure with a large study population are needed in order to examine this association reliably.

Unlike famine exposure in late childhood or early adolescence, there was no effect of prenatal famine exposure on age at menarche in the Dutch Famine Cohort Study of 700 women born during the 1944-45 Dutch Famine [101]. This finding was supported by 2 separate cross-sectional studies in 21 000 Japanese and 653 Chuvashian women that showed a greater effect on age at menarche in women exposed to famine during early adolescence compared to those born during the famine [93, 98].

Adult height

There are two parallel processes of childhood growth: somatic (an increase in the amount of tissue) and maturation (an alteration in tissue function) [102]. Attainment of adult height and menarche are part of the final events in somatic growth and maturation respectively, with attainment of adult height generally occurring after menarche. Adult height is determined at the individual level predominantly by genetics [97], but is particularly sensitive to diet and other environmental factors in early childhood when leg growth is most rapid [103, 104]. Thus it may be used to represent in part the overall nutritional status of an individual throughout childhood to help assess if acute nutritional insults have been overcome by catch-up growth. Most of the existing evidence on the association between adult height and age at menarche comes from small cross-sectional and prospective studies and may be confounded by weight or diet, which are both correlated with age at menarche. On the other hand, age at menarche can also affect adult height, as growth plates fuse in response to the increase in circulating endogenous oestrogen. Hence, it is the pattern of growth in childhood – rather than adult height – that is a more important indicator of pubertal timing. However, as a weak proxy for overall childhood nutritional status, adult height has been shown to be only weakly associated with age at menarche.

Nevertheless, a weak but significant correlation between adult height and age at menarche has been found, ranging from 0.1-0.2 among 2256 American women enrolled in the US National Heart, Lung and Blood Institute Growth and Health Study [105], with a similar correlation in 2780 Danish women [106]. However, it is not clear from these studies whether height influences age at menarche or vice versa. Among 286 205 women from nine countries in The European Prospective Investigation into Cancer and Nutrition, there was a positive association between adult height and age at menarche with an approximate increase in adult height of 0.3cm (range by country: 0.1-0.5 cm) with each year delay in menarche [34]. By contrast, there is very little evidence on the effect of differences in adult height, and therefore long-term childhood nutrition, on age at menarche: a cross-sectional study of 995 Bangladeshi women born in 1979-86 found that age at menarche increased by 0.02 years per cm increase in adult standing height [91].

2.2.3.2 Socioeconomic factors

Most previous studies have found that women with higher SES experience menarche earlier than women with lower SES, despite inconsistent definitions of SES across studies. Both combined measures of SES and individual socioeconomic factors can be interpreted as surrogates for a range of unspecified exposures that are difficult to measure. This makes socioeconomic factors prone to random measurement error and consequently less accurate in measuring true differences in environmental exposure [107]. Thus, studies may be limited by random measurement error attenuating associations towards the null [108] and by reduced sensitivity of combined measures to heterogeneity of SES in the population. However, any real association between age at menarche and SES is likely to be complex. It is highly likely that socioeconomic factors may act through other known correlates of age at menarche [27], such as nutrition, rather than having an independent effect. It is also possible that socioeconomic influences on age at menarche would no longer be seen in populations where mean age at menarche has approached the genetically-determined lower limit.

Single measures of SES used by previous studies include education level, parental occupation and number of siblings. In 2 separate studies of 2644 Ghanaian and 8030 Norwegian women, the most highly-educated women experienced menarche approximately 0.4 years earlier than women with the lowest level of education [109, 110]. Two separate cross-sectional studies of 3206 Columbian and 1017 Turkish women that categorised SES based on parental occupation alone found that women in the lowest SES group had menarche 0.6-0.7 years later than women in the highest SES group [25, 111], whereas a similar study on 516 Portuguese girls found no significant association [112]. Three separate studies looking at number of siblings or family size in more than 3000 women in Columbia, Italy and Nigeria have found a significant delay in menarche of 0.1-0.2 years between the smallest and largest categories [25, 77, 111], whereas two smaller studies of 995 Bangladeshi [91] and 561 Portuguese women [112] failed to detect a significant association, possibly because they were underpowered.

A few other studies have used multiple parameters (e.g. education, occupation and income) to classify SES with mixed results. Two separate cross-sectional studies that used parental education and occupation to derive SES via the Hollingshead Index in 1017 Turkish and 3783 Italian women found no significant association with age at menarche [27, 77]. A cross-sectional study of 955 Venezuelan girls that classified SES based on a composite score for head of household's profession, mother's education level, principal source of income and housing conditions found that mean age at menarche was approximately 0.5 years higher in the lowest compared to the highest SES group [113].

2.2.3.3 Month and season of birth

Results from the two included cross-sectional studies on the association between age at menarche and month or season of birth are inconsistent. In a study of 2992 American women aged 18-25, women born October-December were found to have a mean age at menarche 0.2 years lower than women born in either January-March or April-June [114]. However, a smaller study of 591 American girls aged 8-18 found no such association, but may have been underpowered, especially as not all of the participants had undergone menarche [115].

2.2.4 Summary

There is reasonably good evidence, primarily from the Dutch population, that famine exposure in late childhood or early adolescence is associated with a delay in menarche and suggestive evidence that worsening socioeconomic conditions may have a similar but smaller effect. By contrast, substantial uncertainty remains about the associations between age at menarche and adult height (as a proxy for long-term childhood nutrition) and month or season of birth. Most of the current evidence comes from cross-sectional studies of adult women that may be subject to recall bias and do not establish cause-effect relationships, or from small prospective studies of children and young adults that may be underpowered to detect an association. In addition, none of these associations have been examined on a large scale in developing countries, some of which have undergone rapid changes in female reproductive patterns.

2.3 Age at menopause

During the second half of the 20th century, evidence accumulated from observational studies of both higher rates of cardiovascular disease in postmenopausal compared to premenopausal women [62] and an association between oestrogen exposure and reproductive tract cancers [116]. Consequently, there has been much research on the correlates of age at menopause, with a few larger population-based studies providing better evidence in the last two decades. However, most existing evidence on the topic is derived from studies in the European and American populations, and there is still extremely limited data on developing country populations such as China.

Twenty-nine studies on secular trends and correlates of age at menopause were included in this review, of which 20 were cross-sectional, 7 were prospective cohorts and 2 were retrospective cohorts. Sample sizes ranged from 507 to 33 054 naturally menopausal women, and most of the included studies focused on American and European populations with few studies in developing country populations. In China, the Shanghai Women's Study is the largest study to date on the correlates of age at menopause among 33 054 urban Chinese women aged 40-70 but there are no other studies of a similar size to allow reliable assessment of these associations in other regions of China.

2.3.1 Menopause: timing, physiology and the role of genes

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Clinically, it is recognised as twelve consecutive months of amenorrhoea with no other pathological or physiological cause [117]. Menopause is the only distinct reproductive event marking the exhaustion of follicular reserves and generally occurs between ages 40-60 with a mean of 51 years in most Western countries [118].

Ovarian follicles mature into oocytes that are the source of ovarian oestrogens [119]. The number of primordial ovarian follicles decline steadily from approximately 1 million at birth to approximately 25 000 around age 38 after which there is an apparent acceleration in the rate of decline [117]. Symptoms of hormonal fluctuations such as hot flushes appear and menstrual cycles become irregular on average 4-6 years before the actual menopause [117, 119]. This period is constant irrespective of age at menopause, as the duration of cycle irregularity is dependent on number of remaining ovarian follicles rather than age [117]. Follicles are almost completely depleted at the time of menopause [120] and there is no evidence that ovulation occurs after menses have ceased [119].

The major hormonal changes around the final menses are a progressive elevation of FSH with a concurrent decrease in ovarian oestrogens. Dysregulation of the GnRH pulse generator in the hypothalamus due to progressive lack of neurochemical control from other parts of the brain may, therefore, play an additional role in menopause [117]. After menopause, the cyclical pattern of secretion of gonadotrophins and ovarian oestrogen and progesterone is replaced by persistently elevated gonadotrophins with low levels of ovarian steroid hormones [120].

Despite various estimates of heritability in age at menopause [121-125], on the whole, there is limited and inconsistent evidence on the role of genes in determining age at menopause [126]. Previously, genome-wide linkage analysis found two potentially relevant regions: 9q21.3 (which is associated with a gene that encodes a protein involved in apoptosis) [127] and chromosome 8 at 26 centimorgan (which is associated with the GnRH I gene) [128]. More recently, two GWAS of 2979 European [129] and 17 438 American women [130] found an association between age at menopause and two variants on chromosomes 19q13.42 and 20p12.3 located near genes coding proteins that may be involved in reproductive aging. However, the effect size of any of these alleles on age at menopause has yet to be quantified.

2.3.2 Secular trends

In comparison with age at menarche, information on population secular trends in age at menopause is far more limited. In developed countries, the mean age at menopause seems to have either remained stable or increased at the population level over the 20th century. In a study of 4767 American women aged 60-80, age at menopause increased by 0.6 years per decade [131]. Secular trends in age at menopause in Europe appear to be inconsistent [132], with some countries showing no trend [46, 133] and some showing an increasing trend ranging from 0.1-1.0 years per decade [48, 134-137]. There is very little information from large-scale studies in Asian populations, although a study of 6477 Japanese women reported an initial increase of 0.7 years per decade for women born during 1917-32 followed by a large decrease of 2.4 years per decade for women born during 1933-37 [138].

2.3.3 Correlates of age at menopause

2.3.3.1 Reproductive factors

Though not entirely consistent, there is evidence – predominantly from cross-sectional studies – of an association between age at menopause and a number of reproductive factors that affect oocyte numbers. Gravidity and parity have shown the strongest effect on age at menopause of any reproductive factor whereas evidence on other reproductive factors such as age at menarche, age at first birth, breastfeeding or number of still births, spontaneous abortions or induced abortions has either been less convincing or shown no apparent effect. There is some evidence from larger studies that use of oral contraceptives (OCs), including later age at starting OC use, can delay menopause. Furthermore, there is suggestive evidence that the strength of these associations in Chinese women differs from those of American and European populations, particularly with regards to the effect of breastfeeding and age at first birth. This may be partly due to different reproductive patterns and trends in China as well as the difference in quality and breadth of information on reproductive factors available between different studies.

Age at menarche

Given the finite number of oocytes in a woman, it is possible that a later age at menarche would be linked to a later age at menopause, but studies have produced inconsistent results. Several studies in Iranian [139], European [42, 45, 48, 132, 134, 135, 140, 141] and American women [40, 131, 142] found no association, whereas a significant positive association was reported in several larger studies in 9471 Dutch [136], 2623 Polish [133], 1017 Swedish [137] and 31 834 Italian [46] women, with mean age at menopause increasing by 0.1-0.2 years per year later menarche. In addition, the Shanghai Women's

Study found that Chinese women with age at menarche ≥16 had menopause 0.6 years later than women with age at menarche ≤11 [143]. The smaller studies may have been underpowered to detect weak associations or failed to account for a concurrent decreasing secular trend in age at menarche and increasing or stagnating secular trend in age at menopause by adjusting for age.

Age at first birth

There are inconsistent findings on the association of age at menopause with age at first live birth. Six studies of less than 4000 women showed no association [45, 48, 133, 139, 140, 144], but the number of women in each age range at first birth may have been too small to allow for reliable exploration of the association. By contrast, the 2319 (7%) women in the Shanghai Women's Study who were ≥30 at their first birth had menopause 0.5 years earlier than the 6882 (21%) women who were ≤20 at their first birth [143]. Apart from a large study population, major changes in age at first birth over the 20th century in China may have provided the Shanghai Women's Study with sufficient women in each age range to detect a weak association.

Gravidity and parity

Higher gravidity and parity have been significantly associated with later age at menopause. There is evidence that menopause can be significantly delayed by up to 3 years in women who have ever been pregnant compared to those who have never been pregnant [139], and by up to 3.3 years with increasing number of live births [40, 42, 46, 131-133, 135-137, 139-143, 145, 146], although a few studies found no association [45, 48, 134, 144, 147]. Again, a lower fertility rate, as seen in most developed countries, may result in a narrow range of number of pregnancies and live births in the populations studied, which may restrict the extent to which these associations can be examined. There appears to be no significant association between age at menopause and number of still births [143], spontaneous abortions [134, 139, 143] or induced abortions [143], but this limited evidence comes largely from the Shanghai Women's Study along with two small studies in 948 Iranian and 507 Turkish women.

Breastfeeding

Breastfeeding can cause lactational amenorrhoea – where a woman can potentially not ovulate for up to 6 months – as lactation delays the return to the normal cycle of sex hormone production by the ovaries [148], and so could potentially affect age at menopause. Although 3 small studies of 507 Turkish, 2623 Polish and 1009 German women found no association between breastfeeding and age at menopause [45, 133, 134], the much larger Shanghai Women's Study found that Chinese women who breastfed > 36 months had menopause 0.5 years later than women who had never breastfed [143]. However, these findings may be confounded by parity and socioeconomic status. Breastfeeding history is known to be strongly related to parity so the range of duration of breastfeeding may be smaller in populations with low fertility rates. Furthermore, breastfeeding habits differ with SES and cultural norms, with possibly greater use of formula feeding in developed countries. In the 3 smaller studies, the maximum duration of breastfeeding was limited at 1-2years, whereas almost a quarter of women in the Shanghai Women's Study had breastfed for more than 3 years. These smaller studies may have had too limited a range of exposure and been underpowered to detect the small effect of duration of breastfeeding on age at menopause found by the Shanghai Women's Study.

Use of oral contraceptives

Use of OCs prevents ovulation and so preserves oocyte numbers which may delay menopause. Most of the studies in this review, ranging from 507 to 31 834 women, showed no significant association between age at menopause and ever use of OCs [42, 45, 46, 137, 141, 145, 147], type of OC used [135] or duration of OC use [134, 135]. However, the Shanghai Women's Study found that women who had ever used OCs had menopause 0.5 years later than women who had never used OCs [143]. A similar delay of 0.1 and 0.7 years in age at menopause was also found in two separate studies of 3756 Dutch [48] and 2623 Polish [133] women respectively, with age at menopause increasing with increasing age at starting OCs in the Dutch study [48]. Since its introduction in the 1960s, various changes in OC use have taken place, including changes in dose-strength and other active ingredients, increasing use for purposes other than contraception as well as the availability of alternative hormonal contraception such as the injection. These changes provide several possible reasons why some studies have failed to find an association between OC use and age at menopause. A study of 427 Swedish women aged 20-34 showed good validity of reporting of OC use with the exception of type of OC used [149]; hence, the study examining the effect of different OC strengths in 8701 Dutch women may have been limited by reliance on self-reporting leading to misclassification bias. The same Dutch study as well as a smaller study of 507 Turkish women may have been unable to detect an effect of duration of OC use on age at menopause due to the range of exposure being limited by timing of OC introduction to the population. Furthermore, selection bias may have been an issue in those studies where only a relatively small proportion of the total postmenopausal population had ever used OCs, as this subset may differ from other women in the study. For example, these women may all be higher-earning or from an urban population with greater financial or geographical access to OCs respectively.

2.3.3.2 Behavioural factors

Several behavioural factors such as smoking, alcohol use and soy consumption may affect age at menopause either by influencing oestrogen levels or by direct action on the ovaries. Smoking is thought to affect age at menopause by 3 possible mechanisms: a direct toxic effect on the ovaries, interference with gonadotrophin release and alteration of sex steroid metabolism [44]. There is evidence that women who consume alcohol are exposed to higher levels of oestrogen [150, 151] and consumption of soy products has been shown to lower circulating levels of oestrogen without altering gonadotrophin levels [152, 153]. Very few studies have examined the association of age at menopause with soy consumption, which has a low prevalence in most populations, but a larger number of studies have examined the association with smoking and alcohol use, both of which are common in Western populations. There is good evidence that current smoking is associated with a later age at menopause but evidence on the association of age at menopause with either alcohol use or soy consumption is equivocal.

Smoking

There is a large body of evidence on the association between smoking age at menopause, derived predominantly from European and American populations where the prevalence of smoking is high even among adolescents [154]. In most studies included in this review, current smokers had menopause 0.4-2.0 years earlier than never smokers [40, 42, 45, 46, 48, 132-137, 141, 142, 144, 146, 147, 155-158], including a difference of 0.8 years between current and never smokers in the Shanghai Women's Study [143]. However, in 2 separate studies of 9471 Dutch [136] and 3513 British women [42], ever smokers had menopause 0.7 years earlier than never smokers whereas former smokers appeared to have the same age at menopause as never smokers [40, 45]. This suggests that the inclusion of former smokers under the category of ever smoker may have attenuated the strength of the reported association between ever smoking and age at menopause in some studies. By contrast, 3 separate studies of 10 995 Australian, 948 Iranian and 507 Turkish women [139, 145, 159] showed no significant association between smoking and age at menopause, possibly due to a lack of power given the small sample size as well as a relatively low prevalence of smoking in these populations.

Alcohol use and soy consumption

There does not appear to be a significant association between age at menopause and alcohol use based on 7 separate studies in at least 4700 American, European or Chinese women [45, 131, 133, 134, 143-145] which are populations with a high prevalence of alcohol use even among adolescents [154]. For soy consumption, neither the Shanghai Women's Study [143] nor a smaller study of 1009 German [45] women showed an association with age at menopause but these studies were based in populations with different soy intake patterns. Although the available evidence on alcohol use is more robust, all included studies examining the effects of alcohol use and soy consumption used self-reporting to measure exposure which may lead to reporting bias and misclassification of exposure groups thereby attenuating the strength of any associations towards the null. Further information from large studies with reliable data and a wide range of exposure categories is needed on the association of age at menopause with both these factors.

2.3.3.3 Socioeconomic factors

Evidence about the associations of age at menopause with education, occupation or income is equivocal, with most of the included studies showing no apparent association between age at menopause and any of these factors [40, 45, 133, 134, 139, 144, 145, 147, 157, 160]. Among those studies with significant findings, age at menopause was found to be 0.2-0.9 years later in women with higher compared to primary school education [131, 133, 137, 146] and 0.1-0.6 years later in women with non-manual versus manual occupations [42, 146]. The Shanghai Women's Study found significant associations for each of the 3 socioeconomic factors among 33 054 Chinese women: mean age at menopause was 1.5 years later for tertiary versus primary education, 0.7 years later for high versus low income and 1.0 years later for professional versus manual occupations [143]. Only one small cross-sectional study of 1076 Turkish women found a marginally significant 0.7 year delay in age at menopause in women with ≤5 years of education compared to women with >5 years of education [140]. The inconsistencies in results between different studies may be partly due to use of different measures of each socioeconomic factor in the various studies as well as different distributions of each socioeconomic factor in the populations studied. A limited range of exposures (e.g. if most women are highly-educated and from higher income groups) may also restrict examination of differences in age at menopause between exposure groups. However, as with age at menarche, the most important reason may be differences in other determinants of age at menopause represented by SES (i.e. residual confounding) across various populations.

2.3.3.4 Premenopausal body mass index

Overall, only a few studies have examined the association between premenopausal BMI and age at menopause. Although there was no evidence of an association in the 2 included studies of 507 Turkish [134] and 695 British [161] women, these studies may have lacked sufficient power to detect an association. By contrast, the Shanghai Women's Study found a very weak trend for self-reported BMI at age 20 for 24 648 Chinese women divided into quartiles of approximately 6000 women each, with a small but significant 0.1 year delay in women with BMI≥21.4 at age 20 compared to women with BMI<18 at age 20 and [143]. It is possible that the Shanghai Women's Study may have underestimated the true strength of the association. Although a comparison of 541 British women enrolled in both the Million Women Study and the MRC National Survey of Health and Development showed a high level of validity for body size variables recalled in middle age [162], there may still have been an element of recall bias producing random measurement error and attenuating the association towards the null.

2.3.4 Summary

Evidence on the correlates of age at menopause is limited by the cross-sectional design of most studies on this topic which cannot establish causal relationships. Furthermore, use of self-reporting in middle age to measure exposures extending as far into the past as childhood may have produced random measurement error through misclassification bias, which would attenuate the actual strength of any associations towards the null. However, despite a lack of information on the correlates of age at menopause in developing countries, there is good evidence that higher parity is associated with later menopause, whereas smoking around the time of menopause is associated with a significantly earlier menopause. Although, the evidence of an association between age at menopause and all other reproductive, behavioural, socioeconomic and anthropometric factors is equivocal in European and American populations, results from the Shanghai Women's Study suggest that these factors play a role in age at menopause among urban Chinese women. This difference may be due to the unique reproductive trends in China as well as the increased power to detect associations in the Shanghai Women's Study given its much larger sample size compared to all other studies in this review. However, more information on the correlates of age at menopause is needed in this and other regions of China to corroborate these findings.

2.4 Reproductive factors, anthropometry and blood pressure

Partly to help interpret any observed relationship between reproductive history and CVD, a number of studies have examined the associations between reproductive factors and known CVD risk factors, chiefly BMI and blood pressure. However, the evidence on the association of these CVD risk factors with reproductive factors is rather limited, to some extent because most of the previous studies were relatively small, involving typically less than 6000 participants. Furthermore, little is known about these associations in developing countries.

2.4.1 Age at menarche, anthropometry and blood pressure

A total of 16 studies on age at menarche were included in this review – 9 prospective cohorts and 7 cross-sectional in design – with sample sizes ranging from 794 to 201 872 women. With the exception of 1 cross-sectional study of 9097 Chinese women, all studies were based in North American or European populations.

Both cross-sectional and prospective cohort studies have found an inverse association between age at menarche and adult BMI at different ages which may vary in strength with race. Overall, adult BMI was 0.1-0.5kg/m^2 lower per year later menarche in 3 separate cross-sectional studies of 8080 Canadian, 9097 Chinese and 201 872 American women with no obvious difference in the strength of the association between Chinese and North American women [120, 163, 164]. The strength of the association of age at menarche with BMI in earlier (up to age 37) and later (over age 34) adulthood was comparable: 0.1-

0.6kg/m^2 versus 0.2-0.8kg/m^2 lower per year later menarche in 3 cross-sectional studies of 13 308 British, 101 415 American and 3433 Scottish women [165-167] and 4 smaller prospective studies of 999 to 3433 British, Scottish and Finnish women [168-171]. The differences in BMI between the lowest and highest ages at menarche were also comparable between early and later adulthood, ranging from 2.6-4.0kg/m^2 in 1204 British [172] , 1658 American women [173] and a further two studies of 1179 and 1479 American women enrolled in the prospective Bogalusa Heart Study [174, 175]. Although a difference of 0.4-0.9 kg/m^2 in BMI under age 37 between black and white women was noted by two small studies of 1000 and1500 American women, the studies were inconsistent as to which race showed the larger difference [173, 174], probably due to too small a number of women in each race to examine this difference reliably.

There is controversy over whether the effect of age at menarche on adult BMI is confounded by the association between age at menarche and childhood BMI due to the tracking of BMI from childhood to adulthood. Six prospective studies in Finnish, British and American women found that adjustment for childhood BMI at different ages had varying effects on the inverse association of adult BMI with age at menarche. Two separate studies in 999 and 5700 British women found that the association with adult BMI was attenuated but still significant after adjustment for BMI at ages 4-7 [168, 169], whereas the association became non-significant after adjustment for BMI at ages 9-18 in the same study of 999 British women [168] along with two separate studies of 700 and 3404 Finnish women [170, 171]. Again, differences between races in the effect of the adjustment were noted: the strength of the association with adult BMI was attenuated by over 50% in 771 white women and became non-significant in 408 black women with adjustment for BMI at ages 5-17 (mean age=8.8 years) in the American Bogalusa Heart

Study [174]. Both menarche and changes in anthropometry occur as part of the process of puberty; hence, the different effects of adjustment for BMI in childhood compared to peri-adolescent BMI may be because adjustment for peri-adolescent BMI effectively adjusts out the exposure itself.

There is more limited evidence about the association of age at menarche with other anthropometric measures. Where significant associations were seen, age at menarche was inversely associated with adiposity, with possible racial differences noted again. Mean adult weight was 0.5-0.7kg lower per year later menarche in the cross-sectional analyses of the Nurses' Health Study I and II of more than 100 000 American women [166] as well as a much smaller cross-sectional study of 3433 Scottish women [165]. Specifically, weight before age 37 (i.e. premenopausal weight) was significantly correlated with age at menarche in a small prospective study of 1179 American women (R= -0.21) [174] and differed by 3.5-8.6kg between women with the lowest and highest ages at menarche in a cross-sectional study of 16 392 American women [176] and a smaller prospective study of 2379 American women where differences in black women were 0.8-2.4kg greater than in white women [105]. A cross-sectional study of 9097 Chinese women found that body fat percentage was 0.5% lower per year later menarche [163]. Although a lower adult waist circumference and/or hip circumference with increasing age at menarche was reported in cross-sectional studies of 9097 Chinese [163] and 13 308 British women [167] as well as a prospective study of 1204 British women [172], a small prospective study of 794 Finnish women found that the association between age at menarche and waist circumference became non-significant after adjustment for adult BMI [170]. The two smaller studies of 1204 British and 794 Finnish women did not find a significant association between age at menarche and waist-hip ratio [170, 172].

Studies on the association of age at menarche with systolic and diastolic blood pressure (SBP and DBP) are conflicting: following adjustment for adult BMI, a cross-sectional study of 9097 Chinese women aged 25-64 found no significant association with DBP but SBP was 0.4mmHg higher per year increase in age at menarche [163], whereas a prospective study of 1204 British women aged ~53 found no significant association with SBP but DBP was 4.3mmHg higher in women with the lowest compared to highest age at menarche [172]. By contrast, a prospective study of 794 Finnish women aged 30-39 found no association with either DBP or SBP [170], but may have been underpowered to detect a small residual effect following adjustment for BMI. Although these results suggest that most of the association between age at menarche and blood pressure is accounted for by the association between age at menarche and BMI, there is some evidence from the largest study of 9097 Chinese women of a small effect of age at menarche on SBP independent of BMI.

2.4.2 Age at menopause, anthropometry and blood pressure

Only 2 small studies met the inclusion criteria for this review: a cross-sectional study of 2588 postmenopausal Norwegian women aged 55-74 who participated in a population health survey in Tromso, and a prospective cohort study of 1022 Japanese women aged ≤53 at enrolment in 1958 in the Nagasaki follow-up programme for the Radiation Effects Research Foundation, who were followed up until 10 years after natural menopause. Neither study found a significant association between age at menopause and BMI, SBP or DBP [177, 178]. Notably , in the latter study, differences in BMI and SBP between exposure groups defined by age at menopause persisted from premenopause through menopause and up to 10 years after menopause [178]. For example, at all ages, women with menopause at ages 45-49 had a significantly lower BMI compared to women with menopause at ages ≥50 while mean SBP was progressively higher in later age-at-menopause groups [178]. While menopause did not appear to have an effect on BMI or SBP, the observed differences in these parameters between age-at-menopause groups that tracked from pre- to postmenopause suggest that unknown common determinants of age at menopause, SBP and BMI may have been responsible for the trends observed in this study.

2.4.3 Summary

There is a large body of evidence from cross-sectional and prospective cohort studies in developed countries on the association of age at menarche with BMI, but less is known about its association with other anthropometric measures or blood pressure. In fact, the inverse association of age at menarche with either adult anthropometric measures or blood pressure seen in most studies may be largely accounted for by the strong inverse association of age at menarche with BMI, which is comparable in earlier and later adulthood and varies with race. Based on current evidence, adjustment for early childhood BMI has no effect on the association between age at menarche and adult BMI, whereas adjustment for adolescent BMI attenuates the association completely in most of the smaller studies. Evidence on the association between age at menarche and blood pressure is limited and inconsistent, particularly following adjustment for adult BMI. Based on very limited information, age at menopause does not appear to have an effect on either postmenopausal anthropometry or blood pressure. These studies may be limited by inconsistent definition of exposure categories, reflecting different ranges of age at menarche and menopause in populations, and over half the studies in this review may have been underpowered (< 6000 women) to detect weak associations. Overall, there is insufficient evidence on the association of age at menarche and menopause with blood pressure and anthropometry despite widespread interest in the effect of reproductive history on CVD in women.

2.5 Conclusion

Over the last 30 years, there have been significant changes at the population level in age at menarche and menopause. Observational studies predominantly in developed countries have provided consistent evidence that famine exposure and lower childhood SES are associated with a delay in menarche of up to a year. They have also provided largely consistent evidence that higher parity is associated with up to 3 years delay in menopause whereas current smoking is associated with up to 2 years earlier menopause. However, evidence on all other correlates of age at menarche and menopause is equivocal. Furthermore, there is currently inadequate evidence on the association of age at menarche and menopause with CVD risk factors apart from the association of age at menarche with adult BMI. Notably, there is a dearth of information on these trends and associations in developing countries such as China, where there have been major changes in reproductive trends and a growing burden of chronic diseases. Studies to date have also been limited by small sample sizes that would prevent reliable examination of these weak associations, particularly across sub-groups. The China Kadoorie Biobank provides a unique opportunity to examine these associations in a large Chinese population drawn from ten different areas of China, which has been exposed to the Great Chinese Famine at different life stages and undergone major changes in reproductive and lifestyle trends over the last century.

Table 1. Literature review: Correlates of age at menarche

First author (year)	Study design	Participants	Relevant exposures	Outcome	Main relevant results
➢ Adanu et al (2006)	➢ Cross-sectional	➢ 2644 Ghanaian women aged 18-100 enrolled in the Women's Health Study of Accra, Ghana	➢ Education level ➢ SES	➢ Age at menarche	➢ Women in lowest SES group had menarche 0.31 years later than women in highest SES group – p<0.05 ➢ Women with tertiary education had menarche 0.35 years earlier than women with no education – p<0.05
➢ Albright et al (1990)	➢ Cross-sectional	➢ 591 American girls aged 8-18 registered with the Tremin Trust, USA	➢ Season of birth ➢ Month of birth	➢ Age at menarche ➢ Season of menarche	➢ No significant association between month of birth and age at menarche ➢ No significant association between month or season of birth and season of menarche
➢ Biro (2001)	➢ Prospective cohort	➢ 1092 white and 1164 black American girls aged 9-10 enrolled in NHLBI Growth and Health Study, US – followed up for 10 years	➢ Standing height – measured annually i.e. ages 9/10-19/20	➢ Age at menarche ➢ White participants defined as early versus mid-onset versus late maturers if menarche occurred <11.7, 11.7-13.5 and >13.5 respectively ➢ Black participants defined as early versus mid-onset versus late maturers if menarche occurred <11.0, 11.0-12.9 and >12.9 respectively	➢ Height at age 18 was significantly correlated with age at menarche in both black (R=0.12) and white girls (R=0.15) – p<0.001

➢ Chavarro (2004)	➢ Cross-sectional	➢ 3206 Colombian females aged 15-42 enrolled in undergraduate programmes at the National University of Colombia (Bogota´ campus) between January 1998 -2001	➢ SES based on parental occupation ➢ Number of siblings/Family size ➢ Year of birth	➢ Age at menarche	➢ Women in the lowest SES group had menarche 0.72 years later than women in the highest SES group – $p=0.002$ ➢ Women with 1-2 siblings (family size=3/4) had menarche 0.18 years earlier than women with 4 or more siblings (family size≥7) – $p=0.04$ ➢ Mean age at menarche decreased by 0.46 years per decade – $p<0.001$
➢ Cho et al (2010)	➢ Cross-sectional	➢ 3552 Korean women born 1920-85 who took part in the 2005 Korean National Health and Nutrition Survey	➢ Year of birth	➢ Age at menarche	➢ Age at menarche decreased at a rate of 0.68 (95% CI 0.64-0.71) years per decade from 16.90 years in women born 1920-24 to 13.79 years in women born 1980-85 – $p<0.05$
➢ Ersoy et al (2004)	➢ Cross-sectional	➢ 1017 Turkish girls aged 14-18 at high school in Manisa, Turkey	➢ SES based on Hollingshead index (uses parents' education and occupation)	➢ Age at menarche	➢ No significant association with SES
➢ Farid-Coupal et al (1981)	➢ Cross-sectional	➢ 955 Venezuelan girls aged 9-20 enrolled in the National Human Growth, Nutrition and Family Survey in Carabobo, Venezuela	➢ SES based on a) profession of head of household, b) education level of mother, c) principal source of income and d) housing conditions	➢ Age at menarche	➢ Mean age at menarche differed between the 3 SES groups: 12.86 ± 0.12 versus 12.59 ± 0.11 versus 12.34 ± 0.11 years in the lowest, middle and highest SES group respectively – $p<0.05$
➢ Helm (1995)	➢ Cross-sectional	➢ 2780 Danish women aged 15-44 years in Copenhagen county, Denmark	➢ Adult standing height (self-reported)	➢ Age at menarche	➢ When age was taken into account, adult height and age at menarche were significantly correlated (R = 0.17: p<0.00l)

➢ Helm and Gronlund (1998)	➢ Cross-sectional	➢ 979 Danish girls aged 10-17 in Northern Zealand, Denmark ➢ Comparison populations: In same area of Northern Zealand, 983 and 1591 Danish girls aged 10-17 years in 1965-66 and 1982-83 respectively	➢ Year of birth	➢ Age at menarche	➢ Mean age at menarche in 1966 was 0.37 years later than mean age at menarche in 1983 and 0.40 years later than mean age at menarche in 1996 – $p<0.0001$ ➢ Mean age at menarche did not differ significantly between 1983 and 1996
➢ Hillman et al (1970)	➢ Cross-sectional	➢ 2992 American women aged 18-25: 2006 university students and 896 graduates – data taken from routine admission records of 3 student health services	➢ Season of birth	➢ Age at menarche	➢ Mean age at menarche for women born Oct-Dec was 12.84 years versus women born Jan-Mar (12.99 years) and women born Apr-Jun (13.01 years) – $p<0.05$
➢ Hoel et al (1983)	➢ Cross-sectional	➢ 21 000 Japanese women born 1890-1945 in Hiroshima and Nagasaki, Japan surveyed in 1970 as part of the Atomic Bomb Casualty Commission ➢ Comparison population: 10 000 American women who responded to the National Center for Health Statistics Health Examination Survey between 1960-70	➢ Year of birth	➢ Age at menarche	➢ Overall decrease in mean age at menarche for consecutive birth cohorts of 2 years (16.4 to 14.4 years) for Japanese and 1 year for US women over 45 year period: 0.44 years per decade in Japanese versus 0.22 years per decade in Americans. ➢ Anomalous period of increase in mean age at menarche in 1920-34 cohort of Japanese women whose expected years of menarche were during early 1940s in WWII. Mean age at menarche stagnated between 1920-24 and 1925-29 birth cohorts (15.3 versus 15.2 years) then increased to 15.5 years for the 1930-34 birth cohorts before resuming the downward secular trend.
➢ Hossain et al (2010)	➢ Cross-sectional	➢ 995 Bangladeshi women born 1979-86 from Rajshahi University, Bangladesh	➢ Adult standing height ➢ Year of birth ➢ Number of siblings	➢ Age at menarche	➢ Age at menarche increased by 0.097 years each year 1979-86 (an increase of 0.12 years per decade) – $p=0.046$ ➢ Age at menarche increased by 0.015 years per cm increase in standing height – $p=0.0001$ ➢ Age at menarche increased by 0.018 years per additional sibling – $p=0.586$

➢ Huen et al (1997)	➢ Cross-sectional	➢ 6467 Chinese schoolgirls aged ≥6 in Hong Kong	➢ Year of birth	➢ Age at menarche	➢ Mean age at menarche decreased by 0.47 years between 1962-93 (0.16 years per decade) - $p<0.01$
➢ Hwang et al (2003)	➢ Cross-sectional	➢ 1061 South Korean women born 1920-86 randomly recruited from Ansan Cohort Study sample	➢ Year of birth grouped into decade of birth	➢ Age at menarche	➢ Mean age at menarche decreased by 4.1 years from 16.8 to 12.7 years over 67-year period (0.64 years per decade) – $p<0.0001$ ➢ Decreasing secular trend in mean age at menarche shows stagnation for women born 1930-40 (Authors note that these women experienced WWII and the 1950-53 Korean War through childhood to adolescence)
➢ Jacobsen and Lund (1990)	➢ Cross-sectional	➢ 8030 Norwegian women aged 20-56 enrolled in the Third Tromso Study (general health screening survey), Norway	➢ Education level	➢ Age at menarche	➢ Women with <8 years of education had menarche 0.4 years later than women with >16 years of education – p for linear trend<0.0001
➢ Kac et al (2000)	➢ Cross-sectional	➢ 1955 Brazilian women aged 16-76 born 1920-79 enrolled in the 1996 Nutrition and Health Survey in Rio de Janeiro, Brazil	➢ Year of birth	➢ Age at menarche	➢ Age at menarche decreased from 13.07 years for women born in the 1920s to 12.40 years for women born in the 1970s at a rate of 0.12 years per decade – $p<0.001$
➢ Kalichman (2006)	➢ Cross-sectional	➢ 617 Chuvashian females aged 18-80 years from rural Chuvashia in central Russia	➢ Year of birth – grouped into decades	➢ Age at menarche	➢ Mean age at menarche increased from 15.4 years for women born in the 1910s to 16.5 years for women born in the 1930s. A decreasing secular trend in mean age at menarche was seen for women born 1940 from 15.5 years for women born in the 1940s to 13.0 years for women born in the 1980s (0.63 years per decade). Authors note a period of food-rationing 1941-47 in this region following WWII.

➢ Kalichman et al (2007)	➢ Cross-sectional	➢ 653 native Chuvashian women aged 18-90enrolled in the Chuvasha Skeletal Aging Study	➢ Year of birth ➢ "Expected" age at menarche for women born 1925-36 (i.e. 15 – mean age at menarche of women born 1915-1923	➢ Age at menarche	➢ Mean age at menarche increased from 15.4 years to 16.3 years for women born 1924-29 to 16.5 years for women born 1930-36 before decreasing steadily to 14.0 years for women born 1961-65 ➢ Mean age at menarche for women born 1925-36 was16.65 versus 15.96 years for women born 1937-48 – p=0.005 ➢ Only women whose "expected" age at menarche was during the 1941-47 period of food rationing in the Soviet Union experienced an increase in mean age at menarche
➢ Lumey et al (1997)	➢ Retrospective cohort	➢ 700 Dutch women of lower and intermediate SES aged 41-46 born during the Dutch Famine 1944-45 registered in the Dutch Famine Cohort Study	➢ Degree and timing of prenatal exposure to famine in each trimester	➢ Age at menarche	➢ No significant difference in mean age at menarche when unexposed group was compared to exposure in each of the 3 exposure groups
➢ Onland-Moret (2005)	➢ Cross-sectional	➢ 286 205 European women aged 35-70 born 1915-1964 from 9 European countries enrolled in the EPIC study	➢ Year of birth grouped into 5-year birth cohorts	➢ Age at menarche	➢ Statistically significant downward secular trend in age at menarche in all participating European countries ranging from 0.10 to 0.32 years per decade. ➢ In the Netherlands, Germany and France (in descending order of severity), a sharp temporary increase in mean age at menarche for women born 1920-1934. Downward secular trend resumes in women born 1935 onwards in these countries. Authors note that only the Netherlands and Germany experienced severe famine as a result of WWII.

➢ Ossa et al (2010)	➢ Cross-sectional	➢ 688 indigenous and non-indigenous women in central southern Chile divided into 4 cohorts of 172 women (86 indigenous and 86 non-indigenous): 1960-69, 1970-79, 1980-89 and 1990-96	➢ Year of birth	➢ Age at menarche	➢ Overall, age at menarche fell by4.6 months per decade (0.38 years per decade) between 1960 and 1996 – p<0.001 ➢ Age at menarche fell by 4.8 months (0.40 years) per decade and 4.4 months (0.37 years) per decade for non-indigenous and indigenous women respectively – p<0.001. No interaction between ethnic group and age cohort.
➢ Padez and Rocha (2003)	➢ Cross-sectional	➢ 516 Portuguese girls aged 9-19 at secondary school in Coimbra, Portugal	➢ Parents' education level (primary, secondary or university level) ➢ Number of siblings	➢ Age at menarche	➢ No significant association between age at menarche and either SES factor
➢ Papadimitriou et al (2008)	➢ Cross-sectional	➢ 750 Greek high-school students aged 14-18 enrolled at schools in Greater Athens, Greece ➢ Comparison population: 1134 high-school students enrolled in schools in Greater Athens – same methodology employed by same authors in 1996	➢ Year of birth	➢ Age at menarche	➢ Mean age at menarche was 12.29 years in 2006 versus 12.27 years in 1996 – p=0.73
➢ Prentice et al (2010)	➢ Cross-sectional	➢ 924 Gambian girls aged 9-20 from 3 villages in rural Gambia	➢ Year of birth	➢ Age at menarche	➢ Mean age at menarche decreased by 0.65 (95% CI: 0.37-0.92) years per decade from 16.06 (15.67-16.45) years in 1989 to 15.03 (14.76-15.30) years in 2000 to 14.90 (14.52-15.28) years in 2008 – p<0.0001

➢ Rehan (1994)	➢ Cross-sectional	➢ 5736 Hausa students aged 11-18 from 14 girls' schools in Northern Nigeria	➢ SES based on father's occupation ➢ Number of sisters ➢ Area of residence	➢ Age at menarche	➢ Urban girls experienced menarche 0.56 years earlier than rural girls – p<0.0001 ➢ Girls in highest SES group had menarche 0.63 years earlier than girls in the lowest SES group – p<0.0001 ➢ Girls with >5 sisters had menarche 0.05 years later than girls with 1-2 sisters – p<0.01
➢ Rigon (2010)	➢ Cross-sectional	➢ 3783 high-school students aged 15-21 from 13 cities in Northern Italy and 3 cities in Southern Italy	➢ SES based on Hollingshead index (uses parents' education and occupation) ➢ Family unit size ➢ Year of birth	➢ Age at menarche (in students and their mothers)	➢ No association found between age at menarche and SES ➢ Girls from families with ≥5 members had menarche 0.2 years later than girls from families with ≤3 members – p<0.05 ➢ Students had menarche 0.32 years earlier than their mothers (0.1year per decade decrease) – p<0.0001
➢ Rimpela and Rimpela (1993)	➢ Cross-sectional	➢ 11 219 Finnish girls aged 16-18 born 1960-72 from a nationally representative sample of female adolescents surveyed every 2 years 1979-89 in Finland	➢ Year of birth	➢ Age at menarche	➢ Overall decrease in mean age at menarche was not significant – p=0.13 ➢ Significant regional and urban versus rural differences in mean age at menarche were seen in 1979 (p<0.001) but these differences were not seen in the 1989 survey ➢ Significant decreasing secular trends of 0.28 years per decade (p<0.001) and 0.32 years per decade (p<0.01) for girls living in the North-West region and rural areas respectively.
➢ Rosenberg (1991)	➢ Cross-sectional	➢ 9050 Norwegian women born 1830-1960from Oslo, Bergen and Trondheim – data taken from samples of 200-300 maternity hospital records every 10 years	➢ Year of birth	➢ Age at menarche	➢ Mean age at menarche fell at 2.6 months (0.22 years) per decade over the 130 year period – p<0.05.

➢ Tryggvadóttir et al (1994)	➢ Cross-sectional	➢ 68 558 Icelandic women born 1900-69 surveyed as part of a national cancer screening programme	➢ Year of birth divided into 7 cohorts	➢ Age at menarche	➢ Age at menarche declined from 14.94 ± 0.13 years for women born 1900-09 to 13.54 ±0.03 years for women born 1950-54. No further decline in subsequent cohorts was seen. p<0.001 for fit of regression curve. Overall rate of decline was 3.6 months (0.3 years per decade).
➢ Van Noord et al (1991)	➢ Retrospective cohort study and cross-sectional component	➢ 21 067 Dutch women born 1911-1945 enrolled in breast cancer screening programme residing in Utrecht during 1944-45	➢ Year of birth ➢ Subjective experiences of hunger, cold and weight loss as a measure of severity of famine exposure ➢ Classification of hunger exposure by place of residence during Dutch Famine	➢ Age at menarche	➢ Longitudinal analyses: Mean age at menarche decreased from 14.50 years for women born 1911 to 13.56 years for women born 1945 (0.28 years per decade). An increase in mean age at menarche for women born 1924-30, peaking at 14.40 years for women born 1930, was seen before the secular trend decreased again ➢ Cross-sectional analyses: No significant association between geographical classification of famine exposure and odds of experiencing menarche amongst eligible birth cohorts. Subjective reporting of severity of famine exposure associated with lower odds of experiencing menarche in that year (OR=0.46, 95% CI 0.26-0.83)
➢ Veronesi and Gueresi (1994)	➢ Cross-sectional	➢ 2930 Italian women born 1930-73 in Bologna province, Italy, sampled via 4 surveys over 15 years by University of Bologna Dept of Statistics	➢ Year of birth divided into 5 birth cohorts	➢ Age at menarche	➢ Age at menarche decreased from 12.52 years in the 1930-39 cohort to 12.20 years in the 1950-59 cohort before increasing to 12.53 years in the 1970-73 birth cohort – p<0.001for difference between cohorts. This indicates a levelling-off of the secular trend in age at menarche in this population.

➢ Wyshak (1983)	➢ Cross-sectional	➢ 8822 white middle-class American women born in the first half of the 20th century– data taken from National Mothers of Twins Clubs survey	➢ Year of birth – grouped into 6 cohorts	➢ Age at menarche	➢ Mean age at menarche decreased by 3.2±0.36months (0.27 ±0.03 years) per decade – highly statistically significant (exact p-value not given)

Table 2. Literature review: Correlates of age at menopause

First author (year)	Study design	Participants	Relevant exposures	Outcome	Main relevant results
➢ Adena and Gallagher (1982)	➢ Cross-sectional	➢ 10 995 naturally menopausal Australian women who attended a health referral centre in Sydney for a multiphasic health test	➢ Smoking status	➢ Age at menopause	➢ No significant association with smoking status
➢ Amigoni et al (2000)	➢ Cross-sectional	➢ 5813 naturally postmenopausal Italian women aged 55-66	➢ Smoking status	➢ Age at menopause	➢ Mean age at menopause was 50.4[SD 3.8] years in never smokers versus 50.0[3.8] years in current smokers versus 49.7[4.2] years in ex-smokers – p=0.05
➢ Ayatollahi et al (2002)	➢ Cross-sectional	➢ 948 naturally menopausal Iranian women aged ~48-49	➢ Education level ➢ Smoking status ➢ History of abortion ➢ Age at first birth ➢ Age at menarche ➢ Gravidity ➢ Parity	➢ Age at menopause	➢ No significant association with education, smoking, abortion history, age at first birth or age at menarche ➢ Mean age at menopause was 46.1[SD5.2] years in women with no pregnancies versus 49.1[4.7] years in women with ≥10 pregnancies – p=0.002 ➢ Mean age at menopause was 46.1[5.2] years in women with no live births versus 49.4[4.9] years in women with ≥10 live births – p=0.007

➢ Aydin (2010)	➢ Cross-sectional	➢ 507 naturally menopausal Turkish women aged 44-61 born 1946-62 with no HRT use enrolled in the Isparta Menopause and Health Study	➢ Year of birth ➢ Smoking status ➢ Alcohol use ➢ Education level ➢ Age at menarche ➢ Gravidity ➢ Parity ➢ Number of spontaneous abortions ➢ Breastfeeding ➢ OC use (status and duration) ➢ BMI at age 25	➢ Age at menopause	➢ No significant association with alcohol use, gravidity, parity, age at menarche, number of spontaneous abortions and duration of OC use ➢ Mean age at menopause increased with later year of birth, education, ever use of OCs and between the first and second quartile of BMI at age 25 and decreased with increasing duration of breastfeeding in univariate analyses ➢ In multivariate analyses, only year of birth (HR 0.94, 95% CI 0.92-0.97) and premenopausal smoking (1.37, 1.09-1.72) were significantly associated with age at menopause – $p<0.006$
➢ Beser et al (1994)	➢ Cross-sectional	➢ 1076 Turkish women aged 40-54 in Trabzon	➢ Education level ➢ Urban/rural residence ➢ Parity ➢ Age at menarche ➢ Age at first birth	➢ Age at menopause	➢ No significant association with age at menarche or age at first birth ➢ Mean age at menopause was 46.68[SEM 0.14] years in women with ≤5 years education versus 46.02[0.30] years in women with >5 years education – p=0.05 ➢ Mean age at menopause was 45.58[0.20] years in urban versus 47.74[0.17] years in rural women – p=0.05 ➢ Mean age at menopause was 45.62[0.40] years in women with 0-2 children versus 46.58[0.41] years in women with ≥5 children

Brambilla and McKinlay (1989)	Prospective cohort	660 naturally menopausal American women aged 46.5-56.5 from Massachusetts	Smoking status OC use Education level Income Parity	Age at menopause	No significant association with OC use or parity Mean age at menopause was only significantly associated with smoking status in a multivariate model including education and income: β=0.7988, $p<0.001$ (smokers had menopause earlier than non-smokers)
Cooper et al (1999)	Prospective cohort	543 naturally menopausal American women aged 69-81 enrolled in the Menstruation and Reproductive History Study	Smoking status	Age at menopause	Mean age at menopause was 0.8 (95% CI 0.0-1.5) years lower in current versus never smokers
Cramer et al (1995)	Cross-sectional	8657 naturally menopausal American women aged 45-54	Smoking status Age at menarche Parity	Age at menopause	No significant association with age at menarche Nulliparous women had menopause 0.5 years earlier than multiparous women – $p<0.05$ Smokers had menopause 0.6 years earlier than never smokers – 50.1 versus 50.7 – $p<0.05$
De Vries et al (2001)	Retrospective cohort	8701 Dutch women born 1932-41 living in Utrecht province enrolled in a breast screening programme (DOM) who had no premenopausal HRT use or OC use 4 years prior to menopause	OC use (ever use, duration, use of high-dose OCs i.e. prior to 1972) Smoking status Age at menarche Year of birth Parity	Age at menopause	No significant association with type of OC used, duration of OC use or age at menarche Mean age at menopause was 1.1 years later in women with ≥3 live births versus in women with no live births – 51.2 versus 50.1 years, $p<0.001$ Mean age at menopause was 1.2 years earlier in current smokers than never smokers – 50.0 versus 51.2 years, $p<0.001$ Mean age at menopause increased 0.3 years over the 9 year-of-birth (0.33 years/decade) cohorts – $p<0.001$

➢ Dorjgochoo et al (2008)	➢ Cross-sectional	➢ 33 054 naturally menopausal Chinese women aged 40-70 enrolled in the Shanghai Women's Study	➢ Education level ➢ Family income ➢ Occupation ➢ Age at menarche ➢ Age at first birth ➢ Parity ➢ Breastfeeding ➢ OC use ➢ Number of still births, spontaneous and induced abortions ➢ BMI at age 20 ➢ Total soy consumption ➢ Alcohol use ➢ Smoking status	➢ Age at menopause	➢ No association with number of still births, spontaneous abortions or induced abortions, total soy consumption and alcohol use ➢ Mean age at menopause was 48.7[SD 4.0] years for women with primary education versus 50.2[3.7] years for women with tertiary education – p<0.01 ➢ Mean age at menopause was 48.9[3.5] years in women with low income versus 49.6[3.8] years in women with high income – p<0.01 ➢ Mean age at menopause was 48.8[3.7] years in manual workers versus 49.8[3.7] years in professional women – p<0.01 ➢ Women with age at menarche ≤11 had menopause 0.55 (95% CI 0.1-1.0) years earlier than women with age at menarche ≥16 – p<0.01 ➢ Women aged ≥30 at their first birth had menopause 0.49 (0.3-0.7) years earlier than women aged ≤20 at their first birth – p<0.01 ➢ Women with ≥4 live births had menopause 0.73 (0.5-1.0) years later than women with no live births ➢ Women who breastfed > 36 months had menopause 0.45 (0.3-0.6) years later than women who never breastfed – p<0.01 ➢ Women who had ever used OCs had menopause 0.48 (0.4-0.6) years later than women who had never used OCs – p<0.01 ➢ Women with BMI ≥21.4 at age 20 had menopause 0.22 (0.1-0.4) years later

					than women with BMI<18 at age 20 – p<0.01 ➢ Current smokers had menopause 0.76 (0.5-1.0) years earlier than never smokers – p<0.01
➢ Dratva et al (2009)	➢ Cross-sectional	➢ 5288 European women aged 30-60 born 1940-73 enrolled in either the European Respiratory Health Survey or the Swiss Air Pollution and Lung Disease in Adults Cohort	➢ Year of birth ➢ Age at menarche ➢ Parity ➢ Smoking status	➢ Age at menopause	➢ No significant association with age at menarche ➢ Mean age at menopause increased significantly with higher parity (HR 0.744, 95% CI 0.619-0.894) and was significantly lower by 2 years in current versus never smokers (HR 1.585, 1.273-1.975) ➢ Significant heterogeneity across participating countries for association with year of birth – p<0.001

➢ Elias et al (2003)	➢ Retrospective cohort	➢ 9471 naturally menopausal Dutch women aged 40-73 enrolled in a breast screening programme (DOM), resident in Utrecht during the 1944-45 Dutch Famine	➢ Famine exposure (self-reported severity) ➢ Smoking status ➢ Parity ➢ Age at menarche ➢ Year of birth	➢ Age at menopause	➢ Mean age at menopause was 0.36 (95%CI 0.11-0.60) years later in severely exposed women versus unexposed women – $p<0.05$ ➢ Mean age at menopause occurred 1.83 (0.63-3.03) and 1.30 (0.42-2.18) years earlier in severely exposed women exposed at ages 2-6 and 7-9 respectively – $p<0.05$ ➢ Mean age at menopause was 0.68 (0.52-0.84) years earlier in ever smokers versus never smokers – $p<0.05$ ➢ Mean age at menopause was 0.60 (0.40-0.81) years later in women with ≥1 birth versus women with no births – $p<0.05$ ➢ Mean age at menopause increased by 0.09 (0.05-0.14) years per year increase in age at menarche – $p<0.05$ ➢ Mean age at menopause decreased by 0.014 (0.01-0.02) years per year increase in year of birth (0.14 years/decade)
➢ Fleming et al (2008)	➢ Cross-sectional	➢ 1825 American women aged ≥25 enrolled in the National Health and Nutrition Examination Survey III	➢ Smoking status ➢ Occupation	➢ Age at menopause	➢ No significant association with occupation ➢ Smokers (47.17 years, 95% CI 46.22-48.13) had an earlier menopause than non-smokers (48.59 years, 48.06-49.13) – $p<0.05$
➢ Hardy et al (2008)	➢ Prospective cohort	➢ 695 British women born in 1946 enrolled in the MRC National Survey of Health and Development and followed up until age 57	➢ BMI at ages 15, 20, 26, 36 and 43	➢ Age at menopause	➢ No significant association between age at menopause and BMI at any age

➢ Kaczmarek (2007)	➢ Cross-sectional	➢ 2623 naturally postmenopausal Polish women aged 35-65 enrolled in WOMID (women's health and well-being survey)	➢ Year of birth ➢ Education level ➢ Occupation ➢ Age at menarche ➢ OC use ➢ Age at first birth ➢ Parity ➢ Breastfeeding ➢ Smoking status ➢ Alcohol use	➢ Age at menopause	➢ No association with year of birth, occupation, age at first birth, breastfeeding and alcohol use ➢ Mean age at menopause was 51.0 (95%CI 48.9-53.0) years in women with primary education versus 51.9 (49.4-54.1) years in women with tertiary education – $p<0.0001$ ➢ Mean age at menopause was 51.0 (48.8-53.0) years for women with age at menarche ≤14 versus 51.3 (49.4-54.) years for women with age at menarche ≥14 – $p=0.0003$ ➢ Mean age at menopause was 51.7 (49.5-54.0) years in women who had ever used OCs versus 51.0 (49.5-54.0) years in women who had never used OCs – $p=0.002$ ➢ Mean age at menopause was 51.0 (48.5-52.8) years in women with no live births versus 51.7 (49.0-54.0) years for women with ≥3 live births – $p=0.04$ ➢ Mean age at menopause was 50.7 (48.9-52.7) years in current smokers versus 51.9 (49.2-54.0) years for never smokers – $p<0.0001$

➢ Kato et al (1998)	➢ Prospective cohort	➢ 4694 premenopausal American women aged 34-61 enrolled in New York University Women's Health Study –2035 postmenopausal women	➢ Age at menarche ➢ Parity ➢ Smoking status Education level	➢ Age at menopause	➢ No association with age at menarche or education ➢ Women with no births had menopause at 51.09 versus 51.95 years for women with ≥3 births - RR 0.78 (0.67-0.90), p=0.003 ➢ No difference in mean age at menopause between never and past smokers but current smokers had menopause at 50.80 versus 51.55 years for never smokers –RR 1.28(1.14–1.45), p<0.05
➢ Kaufman et al (1980)	➢ Cross-sectional	➢ 656 naturally menopausal women aged 60-69 from hospitals in America, Canada and Israel	➢ Smoking status	➢ Age at menopause	➢ Mean age at menopause was 49.4 years for never smokers versus 48.0 years for women who smoked 1-14 cigarettes/day – difference= 1.4[SE 0.6] years, p<0.02
➢ Kono et al (1990)	➢ Cross-sectional	➢ 6477 naturally menopausal Japanese women aged 30-70 in Okinawa who participated in a mass uterine cancer screening programme	➢ Year of birth	➢ Age at menopause	➢ Mean age at menopause increased from 48.9[SD 3.83] years in women born ≤1917 to 50.0[3.10] years in women born 1928-32 (0.73 years/decade) then decreased to 48.8[2.47] years in women born 1933-37 – p<0.05
➢ Lawlor et al (2003)	➢ Cross-sectional	➢ 3513 naturally menopausal British women aged 60-79 enrolled in the British Women's Heart and Health Study	➢ Occupation (manual versus non-manual) ➢ Smoking status ➢ Age at menarche ➢ Parity (ever and number of live births) ➢ OC use	➢ Age at menopause	➢ No significant association with age at menarche, number of live births or OC use ➢ Mean age at menopause was 0.55 (95%CI 0.17-0.94) years lower in women with manual versus non-manual occupations – p=0.002 ➢ Mean age at menopause was 0.68 (0.35-1.00) years earlier in ever versus never smokers – p<0.001 ➢ Mean age at menopause was 1.09 (0.52-1.66) years earlier in women who had never given birth versus those who had at least one birth

➢ Meschia et al (2000)	➢ Cross-sectional	➢ 4300 naturally menopausal Italian women aged ≥55 enrolled in the ICARUS study	➢ Education level ➢ Smoking status ➢ Age at menarche ➢ OC use ➢ Parity	➢ Age at menopause	➢ No association with education, age at menarche or OC use ➢ Smokers had menopause at 50.4[SE0.2] years versus 50.9[0.1] years for non-smokers – p=0.01 ➢ Women with ≥5 births had menopause at 50.9[0.3] years versus 50.0[0.2] years in women with no births – p<0.01
➢ Nagel et al (2005)	➢ Prospective cohort	➢ 5110 German women aged 35-65 followed up for 5.8 years in Heidelberg – 1009 naturally menopausal women	➢ Education level ➢ Parity ➢ Age at first birth ➢ Breastfeeding ➢ OC use ➢ Smoking status ➢ Age at menarche ➢ Alcohol use ➢ Soy consumption	➢ Age at menopause	➢ No significant association with education, parity, breastfeeding, OC use, age at menarche, alcohol use and soy consumption ➢ Mean age at menopause was higher in women aged ≥32 at their first birth versus women aged <20 – HR 0.69 (95% CI 0.51-0.94), p for trend=0.11 ➢ Current smokers had menopause earlier than never smokers (HR 1.40, 1.13-1.58) but ex-smokers were the same as never smokers
➢ Navarro et al (2010)	➢ Cross-sectional	➢ 1225 postmenopausal Spanish women aged 45-85 enrolled in various epidemiological studies in the bone metabolic unit at Insular University Hospital	➢ Annual income	➢ Age at menopause	➢ No significant association with annual income
➢ Nelishan Carda et al (1998)	➢ Cross-sectional	➢ 1500 postmenopausal Turkish women aged 41-70 who were attending a menopause centre in Ankara	➢ Education level ➢ Occupation ➢ Smoking status ➢ Alcohol use ➢ OC use	➢ Age at menopause	➢ No significant association with smoking, alcohol use, OC use, occupation or education ➢ Higher parity was associated with higher age at menopause – p=0.0397 (no effect size given)

➢ Nichols et al (2006)	➢ Cross-sectional	➢ 4767 naturally menopausal American women aged 60-80 born 1910-39 with no HRT use who acted as controls in 3 consecutive population-based case-controls studies in Massachusetts for the Collaborative Breast Cancer Study	➢ Age at menarche ➢ Parity ➢ Education level ➢ Year of birth ➢ Alcohol use	➢ Age at menopause	➢ No significant association with age at menarche or alcohol use ➢ Mean age at menopause increased with higher education and parity – $p<0.05$ ➢ Mean age at menopause was higher in never smokers versus current smokers – $p<0.05$ ➢ Mean age at menopause increased by 1.4 years from 49.1 years in women born 1915 to 50.5 years in women born 1939 (0.58 years/decade) – $p=0.001$
➢ Pakarinen et al (2010)	➢ Cross-sectional	➢ 3944 Finnish women aged >40 enrolled in the National FINRISK Study 1997/2007 who were naturally menopausal between age 25 and 65 and had no premenopausal HRT use	➢ Education level ➢ Occupation ➢ Age at first birth ➢ Parity ➢ Smoking status ➢ Alcohol use	➢ Age at menopause	➢ No significant association with education, occupation, parity, age at first birth or alcohol use ➢ Mean age at menopause was 0.80 (95% CI 0.17-1.40) years earlier in smokers than non-smokers – $p=0.013$
➢ Parazzini et al (2007)	➢ Cross-sectional	➢ 31 834 naturally menopausal Italian women aged ≥55	➢ Year of birth (in 3 cohorts) ➢ Education level ➢ Smoking status ➢ Age at menarche ➢ Parity ➢ OC use	➢ Age at menopause	➢ No significant association with year of birth or OC use ➢ Mean age at menopause was 51.3 years for women with more than high school education versus 51.1 years for women with low education – $p<0.05$ ➢ Current smokers had menopause at 51.0 years versus 51.2 years for non-smokers – $p<0.05$ ➢ Mean age at menopause was 51.1 years for women with age at menarche<11 versus 51.3 years for women with age at menarche>15 – $p<0.05$ ➢ Women with >2 births had menopause at 51.2 versus 50.9 for women with 0 births – $p<0.05$

➢ Rodstrom et al (2003)	➢ Prospective cohort	➢ 1017 naturally menopausal Swedish women born 1908-30 enrolled in the Prospective Population Study of Women in Gothenburg and followed up till 1992-93	➢ Year of birth ➢ Smoking status ➢ Parity ➢ Age at menarche ➢ Education level ➢ OC use	➢ Age at menopause	➢ No significant association with OC use ➢ Mean age at menopause increased with higher parity (β=0.30[SE0.09]), age at menarche (β=0.20[0.09]) and education (β=0.53[0.27]) ➢ Mean age at menopause was 1.44[0.24] years earlier in current smokers than never smokers ➢ Mean age at menopause increased by 0.1[0.02] years per year of birth (1 year/decade)– p<0.0001
➢ Van Noord et al (1997)	➢ Prospective cohort	➢ 3756 naturally menopausal Dutch women aged 59-73 born 1911-25 participating in a population-based breast screening programme (DOM)	➢ Age at menarche ➢ Parity ➢ Age at first birth ➢ OC use ➢ SES ➢ Year of birth ➢ Smoking status	➢ Age at menopause	➢ No association with age at menarche, parity or age at first birth ➢ Increasing secular trend in mean age at menopause of 0.156 years per 10 year-of-birth cohorts (0.16 years/decade) – p=0.002 ➢ Among OC non-users, mean age at menopause decreased with current smoking (β=-0.08, p=0.00) and increased with SES (β=0.05, p=0.01) ➢ Among only OC users, mean age at menopause increased with age started OC use (β=0.22, p=0.00) ➢ Among all women, mean age at menopause increased with SES (β=0.04, p=0.03) and OC use (β=0.09, p=0.00) and decreased with current smoking (β=-0.08, p=0.00)

➢ Velez et al (2010)	➢ Cross-sectional	➢ 4056 women aged 60-79 from Latin America and the Caribbean enrolled in the SABE project	➢ Education level ➢ Occupation ➢ Parity ➢ Smoking status	➢ Age at menopause	➢ Mean age at menopause was lower in women with at most primary education versus women with at least secondary education – HR 1.16 (95% CI 1.07-1.26) ➢ Mean age at menopause was lower in women with manual versus non-manual occupations – HR 1.12 (1.03-1.20) ➢ Mean age at menopause was lower in current smokers versus never smokers – HR 1.14 (1.03-1.27) ➢ Mean age at menopause was lower in women with no children versus women with 1-4 children – HR 1.14(1.02-1.28)

Table 3. Literature review: Reproductive history and CVD risk factors

First author (year)	Study design	Participants	Relevant exposures	Outcome	Main relevant results
➢ Akahoshi (2001)	➢ Prospective cohort	➢ 1022 naturally menopausal Japanese women aged ≤53 in 1958 living in Nagasaki enrolled in the follow-up programme for the Radiation Effects Research Foundation – biennial examinations since 1958	➢ Age at menopause - ≤44 (n=48), 45-49 (n=388) and ≥50 (n=578)	➢ BMI ➢ SBP	➢ Differences in BMI and SBP between age at menopause groups observed in the premenopause, persisted to early (≤ 4 years after menopause) and late menopause (5-10 years after menopause) ➢ Mean (SD) BMI was 22.66 (3.4) kg/m^2 in women with age at menopause 45-49 versus 23.17 (3.3) kg/m^2 in women with age at menopause ≥50 in late menopause – $p<0.01$ ➢ Mean SBP increased by approximately 6mmHg from women with age at menopause ≤44 to 45-49 and by another 5mmHg to women with age at menopause ≥50 in late menopause – $p<0.01$
➢ Biro (2001)	➢ Prospective cohort	➢ 1166 white and `1213 black American women aged 19-20 at baseline enrolled in the NHLBI Growth and Health Study - followed up annually for 10 years from age 9-10	➢ Age at menarche – early (<11.7 for white and <11.0 for black women) and late (>13.5 for white and >12.9 for black women)	➢ Weight at age 18	➢ Age at menarche was significantly correlated with weight in black and white women (R=-0.14, $p<0.001$) ➢ Mean differences in weight between early and mid-onset or late menarche among white women were 3.5kg and 6.2kg respectively – $p<0.001$ ➢ Mean differences in weight between early and mid-onset or late menarche among black women were 4.3kg and 8.6kg respectively – $p<0.001$
➢ Burke et al (1992)	➢ Cross-sectional	➢ 1385 black and 1273 white American women aged 18-30 enrolled in the Coronary Artery Risk Development in Young Adults Study	➢ Age at menarche	➢ BMI	➢ Mean BMI was 24.1 kg/m^2 versus 27.6 kg/m^2 in black women with menarche at age 14-19 versus age 8-11(difference=3.5 kg/m^2) and 21.9kg/m^2 versus 24.5kg/m^{2}in white women with menarche at age 14-19 versus age 8-11 (difference=2.6 kg/m^2)

➢ Feng (2008)	➢ Cross-sectional	➢ 9097 Chinese women aged 25-64 without any chronic diseases from Anhui province, China	➢ Age at menarche	➢ BMI ➢ WC ➢ BFP ➢ SBP ➢ DBP	➢ BMI decreased by 0.127 (SE 0.02) kg/m^2 per year later menarche – $p<0.001$ ➢ WC decreased by 0.355 (0.06) cm per year later menarche – $p<0.001$ ➢ BFP decreased by 0.501 (0.05) % per year later menarche – $p<0.001$ ➢ Significant association with SBP found only after adjustment for BMI: SBP increased by 0.375 (0.12) mmHg per year later menarche – $p<0.001$ ➢ No significant association with DBP
➢ Freedman et al (2003)	➢ Prospective cohort	➢ 408 black and 771 white American women aged ≤37 enrolled in the Bogalusa Heart Study – followed up on average 5 times from age 5	➢ Age at menarche	➢ Weight ➢ BMI	➢ Age at menarche was significantly correlated with weight (R=-0.21) and BMI (R=-0.23-4) – $p<0.001$ ➢ Difference in mean BMI was 3.2-3.6kg/m^2 between menarche at age <12 versus ≥13.5 which was attenuated to 1.4kg/m^2 ($p<0.05$) in white women and became non-significant (0.8 kg/m^2) in black women when adjusted for childhood BMI (age range=5-17, mean=8.8)
➢ Frontini (2003)	➢ Prospective cohort	➢ 1479 black and white American women enrolled in the Bogalusa Heart Study – 6 cross-sectional surveys of children aged 5-17 and 5 cross-sectional surveys of adults aged 18-37	➢ Age at menarche	➢ BMI at age 19-37	➢ Mean BMI was 30kg/m^2 in women with menarche at age <12 versus 26 kg/m^2 in women with menarche at age ≥12 (difference=4kg/m^2)– $p<0.001$

Garn (1986)	Cross-sectional	16 392 white American women aged 20-34 enrolled in the National Collaborative Perinatal Project 476 white American women aged 20-34 enrolled in the Tecumseh health survey of the University of Michigan	Age at menarche – early (≤11), intermediate (12-13) and late (≥14)	Weight BMI	Mean (SD) weight was 56.96 (10) kg and 60.8 (10) kg versus 61.17 (12) kg and 64.6 (11.4) kg in late versus early menarche in the NCPP and Tecumseh surveys respectively (difference=4.2kg and 3.8kg respectively) – p=0.001for both Mean (SD) BMI was 21.66 (4) kg/m^2 versus 23.58 (5) kg/m^2 in late versus early menarche in NCPP survey (difference=1.92 kg/m^2) – p=0.001
Hardy (2006)	Prospective cohort	1204 British women aged ≤53 born in March 1946 enrolled in the MRC National Survey of Health and Development – followed up 21 times from birth to age 53	Age at menarche	SBP DBP BMI WC HC WHR	No significant association with SBP or WHR Significant association with DBP found only after adjustment for BMI: DBP increased by 4.3 (95% CI 1.8-6.9) mmHg from women with menarche ≤12 years 3 months to women with menarche ≥14 years 7 months – p=0.006 BMI decreased from 28.7 (28.1-29.3) kg/m^2 in women with menarche ≤12 years 3 months to 25.8 (24.7-26.8) kg/m^2 in women with menarche ≥14 years 7 months (difference=2.9 kg/m^2) – p<0.0001 WC decreased from 87.1 (85.7-88.5) cm in women with menarche ≤12 years 3 months to 83.3 (80.9-85.7) cm in women with menarche ≥14 years 7 months (difference=3.8cm) – p=0.0004 HC decreased from 108.0 (106.8-109.3) cm in women with menarche ≤12 years 3 months to 103.5 (101.7-105.3) cm in women with menarche ≥14 years 7 months (differences=4.5cm) – p<0.0001
Harris (2008)	Cross-sectional	8080 Canadian women aged ≥15 who took part in the Canadian Community Health Survey 2.2	Age at menarche	BMI	Mean BMI decreased by 0.508 (95% CI 0.236-0.780) kg/m^2 per year later menarche – p<0.0001

➢ He et al (2009)	➢ Cross-sectional	➢ 101 415 American women aged 34-59 enrolled in the Nurses' Health Study (NHS) and 100 457 women aged 26-46 years enrolled in the Nurses' Health Study II (NHS II)	➢ Age at menarche	➢ BMI (self-reported) ➢ Weight (self-reported)	➢ Mean (95% CI) BMI decreased by 0.20 (0.18-0.22) kg/m^2 per year later menarche in the NHS – p<0.0001 ➢ Mean (95% CI) weight decreased by 0.50 (0.44-0.55) kg per year later menarche in the NHS – p<0.0001 ➢ Mean (95% CI) BMI decreased by 0.26 (0.24-0.28) kg/m^2 per year later menarche in the NHS II – p<0.0001 ➢ Mean (95% CI) weight decreased by 0.65 (0.60-0.70) kg per year later menarche in the NHS II – p<0.0001
➢ Joakimsen et al (2000)	➢ Cross-sectional	➢ 2588 postmenopausal Norwegian women aged 55-74 who participated in a population health survey in Tromso, Norway	➢ Age at menopause	➢ SBP ➢ DBP ➢ BMI	➢ No significant association with SBP, DBP or BMI
➢ Kivimaki (2008)	➢ Prospective cohort	➢ 794 Finnish women aged 9-18 at baseline and followed up till age 30-39 as part of the Cardiovascular Risk in Young Finns study	➢ Age at menarche	➢ BMI ➢ WC ➢ WHR ➢ SBP ➢ DBP	➢ No significant association with DBP ➢ Associations with WC, WHR and SBP non-significant after adjustment for BMI ➢ BMI decreased by 0.10 (0.01-0.19) kg/m^2 per year later menarche – p=0.03 ➢ Association with BMI non-significant following adjustment for BMI at ages 9-18
➢ Laitinen et al (2001)	➢ Prospective cohort	➢ 3404 Finnish women aged ≤31 born end of 1965 to beginning of 1967 enrolled in the Northern Finland birth cohort for 1966	➢ Age at menarche	➢ BMI at age 31	➢ Mean BMI (95% CI) at age 31 decreased by 0.56 (0.45-0.68) kg/m^2 per year later menarche which became non-significant with adjustment for BMI at age 14
➢ Lakshman (2008)	➢ Cross-sectional	➢ 13 308 British women aged 40-75 enrolled in the EPIC-Norfolk study with age at menarche in range 8-18	➢ Age at menarche	➢ BMI ➢ WC	➢ Mean (95% CI) BMI decreased by 0.43 (0.38-0.48) kg/m^2 per year later menarche – p<0.001 ➢ Mean WC decreased by 0.74 (0.62-0.85) cm per year later menarche – p<0.001

➢ Okasha (2001)	➢ Cross-sectional	➢ 3433 Scottish women aged 16-30 born 1919-52 who attended health checks at the University of Glasgow	➢ Age at menarche	➢ Weight ➢ BMI	➢ Mean (95% CI) weight decreased by 0.452 (0.236-0.668) kg per year later menarche – p<0.001 ➢ Mean (95% CI) BMI decreased by 0.294 (0.223-0.365) kg/m^2 per year later menarche – p<0.001
➢ Pierce and Leon (2005)	➢ Prospective cohort	➢ 3743 Scottish women aged 45-52 born 1950-55 enrolled in the Aberdeen Children of the 1950s Cohort Study	➢ Age at menarche	➢ BMI	➢ Mean (95% CI) BMI decreased by 0.64 (0.50-0.78) kg/m^2 per year later menarche which was attenuated by 11% to 0.57 (0.43-0.71) with adjustment for BMI at ages 4-7- p<0.001 for both
➢ Pierce et al (2010)	➢ Prospective cohort	➢ 999 British women aged ≤53 born in March 1946 enrolled in the MRC National Survey of Health and Development - followed up 21 times from birth to age 53	➢ Age at menarche	➢ BMI	➢ Mean (95% CI) BMI decreased by 0.75 (0.48-1.00) kg/m^2 per year later menarche (p<0.001) which was attenuated to 0.52 (0.25-0.79) kg/m^2 when adjusted for BMI at age 7 (p<0.001) and became non-significant when adjusted for BMI at age 11 (p=0.09)
➢ Power et al (1997)	➢ Prospective cohort	➢ 5700 British women aged ≤33 born in one week in March 1958 enrolled in the 1958 British birth cohort	➢ Age at menarche	➢ BMI at age 33	➢ Mean (SD) BMI was 26.6 (5.7) versus 22.5 (3.7) in women with menarche at age ≥15 versus ≤11 (p=0.002) which was reduced but still significant after adjustment for BMI at age 11 or age 16

Chapter 3. Study objectives

The main objectives of this study are to:

1. Describe the baseline characteristics of Chinese women born in 1930-1974 enrolled in the China Kadoorie Biobank, with particular emphasis on secular and age-related trends and regional variations;
2. Examine the associations of age at menarche with adult demographic, behavioural and physical characteristics in the total study population;
3. Examine the associations of age at menopause with adult reproductive, demographic, behavioural and physical characteristics in a subset of women who had already undergone natural menopause at the baseline;
4. Present preliminary analyses on the associations of both age at menarche and age at menopause with adiposity and blood pressure as known CVD risk factors; and
5. Comment on the quality of information available on reproductive history and areas requiring further work in the China Kadoorie Biobank

With an extremely large sample size, high quality data on a wide range of variables and large heterogeneity across different study areas, it is expected that this study will make a number of contributions to the literature and further development of the main project, namely:

1. The provision of large-scale evidence about the rapidly changing patterns of reproductive factors in Chinese women over a period in the 20th century which included the introduction of compulsory family planning in China;
2. The provision of reliable observational evidence as to which correlates of age at menarche and age at menopause are relevant to a Chinese population;

3. The provision of preliminary observational evidence about the associations of age at menarche and menopause – the major physiological events determining a woman's reproductive lifetime – with selected CVD risk factors;
4. The suggestion of how the information recorded on reproductive history in China Kadoorie Biobank may be improved in future re-surveys as the minor, methodological component

Chapter 4. Study design and methods for data collection and analysis

4.1 Study design

The China Kadoorie Biobank (CKB) is a large prospective cohort study examining environmental and genetic determinants of common chronic diseases in 0.5 million Chinese men and women. It was established jointly by Oxford University's Clinical Trials Service Unit (CTSU) and the China Centre for Disease Control and Prevention, Beijing [179]. The study cohort was not designed to be representative of the general population in China. Instead, it was planned that participants would be drawn from diverse regions throughout China with a broad range of socioeconomic backgrounds, different disease profiles and a wide range of exposure to risk factors. As an example, the chronic diseases normally associated with affluence (e.g. diabetes and lung cancer) are more prevalent in the urban and coastal regions such as Harbin and Qingdao, whereas the chronic diseases associated with poverty (e.g. chronic obstructive pulmonary disease and oesophageal cancer) are more prevalent in the inland and rural areas such as Sichuan and Henan.

4.2 Baseline survey and re-survey

4.2.1 Data collection

The baseline survey ran from 2004-8 and assessment centres were established in 10 designated areas of China (Figure 1). All potentially eligible participants in these areas were identified through public records and invited to attend. As a prerequisite for participating, all study participants had their unique 18-digit national identity number recorded for future follow-up. Each participant was required to give written consent for blood to be stored long-term and used for non-specific medical research purposes, before undergoing a range of physical measurements and a face-to-face interview with a trained field-worker using a standardised questionnaire (Appendix B). Information was recorded immediately in the assessment clinic using a computer with a direct data-entry system developed specifically for the project, which had built-in functions to pre-empt missing items and minimise logical errors, and help buttons to facilitate interview procedures. The data from each clinic were transmitted daily to the international co-ordinating centre at the CTSU for further checks and statistical monitoring.

Within 2-4 weeks of the initial survey in each area, 15 700 participants were recruited for a quality control survey that included a repeat questionnaire on selected variables including reproductive history for women. These repeat measurements for a random sub-sample (3%) of participants provided estimates of reliability and checks against any serious organisational failure. The first comprehensive re-survey of 25 000 participants, which started immediately following completion of the baseline survey in each area, had a response rate of over 80% and was completed by the end of 2008. A second re-survey of similar size will be conducted during 2012-3, using similar procedures. The re-surveys consist of a questionnaire (almost identical to the baseline questionnaire), full physical examination and blood collection. As with the baseline survey, the data collection, monitoring and management will be done electronically. After completion of the re-survey, attempts will be made to contact a random sample of 10% of non-responders in each area to ascertain reasons for non-response.

Of the 515 681 men and women who attended the baseline survey and completed a consent form, 261 (0.05%) did not complete all stages of the baseline survey, 2209 (0.4%) were subsequently found to have attended the baseline survey more than once, and 311 (0.06%) were found to be outside the required age ranges (30-79 years) at the time of enrolment. Of the 512 900 remaining participants, 302 180 women born in 1930-74 were eligible for analysis in this study.

4.2.2 Study population

302 180 women born in 1930-74 with a known age at menarche were included in the analyses for the baseline description, correlates of age at menarche and association of age at menarche with selected CVD risk factors. Of these women, 158 772 women (approximately 53%) had undergone menopause at the time of baseline survey. However, only 89 320 women (approximately 30%) with natural menopause were included in the analyses for the correlates of age at menopause and the association of age at menopause with selected CVD risk factors after the following exclusion criteria were applied:

- hysterectomy or oophorectomy prior to age at menopause (surgical menopause); or
- age at baseline survey <57 (Of the women aged ≥57 years, 99% reported being postmenopausal, 0.5% perimenopausal and 0.5% premenopausal).

These criteria were chosen to avoid including women under age 57 who had menopause at unusually early ages – although there are still women aged >57 years in the analyses who had menopause at early ages – and excluding women who had not yet had menopause but were likely to do so around age 57. The specific number of women included in various analyses varies due to missing data for a few women and is explicitly stated in the results section.

12 022 women born in 1930-74 who participated in both the baseline survey and the first re-survey were included in the data quality analyses.

4.3 Statistical methods

4.3.1 Range of information from baseline survey

All variables were self-reported with the exception of physical characteristics which were measured at the time of the baseline survey. Information was collected on demographic, socioeconomic and behavioural factors for all participants (Appendix B). Women were asked about reproductive history including age at menarche and menopause, gravidity and parity, duration of breast-feeding for each live birth, OC use, and history of hysterectomy, ovarian or breast surgery (Appendix B).

4.3.2 Definitions

Table 1 contains a list of all major and minor variables and Table 2 contains the definitions of demographic, behavioural and socioeconomic categories examined in this thesis. Definitions of reproductive variables are detailed separately below. When variables were reclassified (e.g. occupation), the revised categories were used consistently throughout the analyses. For variables with an ordinal scale (e.g. number of siblings), values were often collapsed into categories so that there were sufficient women in each category for the statistics to be reliable. Numbers of women in each category are indicated in the results where applicable.

Definitions of reproductive factors

Gravidity is the number of pregnancies. *Parity* is the number of third trimester births and includes live births and still births. *Spontaneous abortions* are accidental miscarriages where a foetus is born before the end of the second trimester and cannot survive *ex utero*. *Induced abortions* are medically or surgically induced miscarriages of a foetus before the end of the second trimester in order to terminate the pregnancy. (Note: in this study, the numbers of spontaneous and induced abortions are included as exposures under the heading *gravidity and parity*).

Oral contraceptive use refers to use of the oral contraceptive pill as a means of preventing pregnancy (i.e. chronic regular use).

Early menarche refers to menarche before age 13 and *late menarche* refers to menarche after age 18. Categories of early and late menarche were chosen using the distribution of age at menarche in the study population. Approximately 90% of CKB women experienced menarche between ages 13 and 18, which is similar to the accepted range of 5-6 years in Western populations [180].

Respondents were categorised as premenopausal or postmenopausal, with postmenopausal further sub-categorised as of either natural or surgical origin.

Premenopausal: Woman with intact uterus and ovaries who answered "No" to "Have you had your menopause?"

Postmenopausal (natural): Woman with intact uterus and ovaries or with an age at hysterectomy/oophorectomy later than age at menopause who answered "Yes" to "Have you had your menopause?"

Postmenopausal (surgical): Woman with age at oophorectomy or hysterectomy earlier than age at menopause. (Note: women with age at hysterectomy ≤ age at menopause cannot be placed under natural menopause as it is not possible to determine age at natural menopause accurately since menses would have stopped at time of surgery).

4.3.3 Analysis

4.3.3.1 Data quality

Spearman correlation coefficients were used to check the level of agreement between the baseline and re-survey measurements of physical characteristics in each area, then area-adjusted correlation coefficients were calculated separately for urban and rural regions and overall. Intra-class correlation coefficients were calculated to check the level of agreement between the baseline and re-survey reporting of all famine exposure variables, age at menarche, age at menopause, number of pregnancies and OC use variables in each area. Weighted kappas, which express the proportion of repeat observations that agree over and above that which would be expected by chance alone [181], were used to check the level of agreement between the baseline and re-survey parity variables in each area.

The following interpretation of weighted kappas was used [182]:

Level of agreement	Weighted kappa
Poor	<0.20
Fair	0.20-0.40
Moderate	0.40-0.60
Good	0.60-0.80
Very good	0.80-1.00

Weighted averages of the area-specific intra-class correlation coefficients or weighted kappa statistics were calculated separately both overall and by urban and rural region [183].

4.3.3.2 Baseline description

Selected demographic, reproductive, behavioural and physical characteristics were described separately for urban and rural regions, and overall. The distribution of each variable, unadjusted means with standard deviations (SD) for continuous variables and unadjusted proportions for categorical variables were presented for all women and by urban and rural residence. To examine age-related trends in physical characteristics, area-adjusted means with 95% confidence intervals (95%CI) were plotted against baseline age in urban and rural populations separately. Means were calculated using the method of least squares, and adjusted to the distribution of areas within the whole study population.

4.3.3.3 Correlates of age at menarche and menopause

The distribution of age at menarche and menopause in the study population was described and the mean age at menarche or menopause by area and year of birth calculated. Heterogeneity between areas (urban versus rural, northern versus southern and inland versus coastal) was examined using conventional tests [184]. In addition, associations with the following variables were examined:

Menarche	Menopause
- Famine exposure – exposure to food shortage, disease/weight loss associated with food shortage, year of worst food shortage	- Reproductive factors – gravidity and parity, oral contraceptive use, age at menarche, age at first birth, breastfeeding
- Standing height as a proxy for chronic childhood nutrition	- Behavioural factors – soy consumption, smoking, alcohol use
- Socioeconomic status – occupation, level of education, number of siblings	- Socioeconomic status – occupation, level of education, annual household income
	- Body mass index at age 25

Means were adjusted for year of birth (as a categorical variable with age at menarche and as a continuous variable with age at menopause) and to the distribution of areas within the whole study population, for subgroups of the characteristic of interest. In addition, for some associations, means were adjusted for other categorical variables considered possible confounders, which is noted in the results. To investigate trends, these adjusted means

(95%CI) were plotted against the mean value of the relevant sub-group (exposure) and a regression analysis was done of individual age at menarche or age at menopause (as appropriate) on individual exposure adjusted for year of birth, area and possible confounders. For categorical characteristics, the adjusted mean (95%CI) for each category was tabulated and the difference (95%CI) between the highest and lowest sub-groups calculated. To examine formally differences in means between sub-groups, a test for trend was used where there was a natural ordering of the sub-groups and a test for heterogeneity was used where there was none [184, 185]. A two-sided p-value was calculated for all differences, tests for trend and tests for heterogeneity.

4.3.3.4 Association of age at menarche and menopause with CVD risk factors

To examine secular trends, area-adjusted means (95%CI) for SBP and DBP, height, current BMI, weight, body fat percentage (BFP), waist circumference (WC), hip circumference (HC) and waist-hip ratio (WHR) were plotted against year of birth as a categorical variable. The range of the y-axis for each figure represents 3 SDs (1.5 SDs in each direction from the overall mean) for that variable. Initially, secular trends for each variable were then plotted separately for each area to look for regional variation. If the trends looked similar between the areas, they were then presented separately (but on the same figure) for urban and rural populations. To examine associations of SBP, DBP, current BMI, BFP, WC, HC and WHR with age at menarche, means (95%CI) adjusted for year of birth and area were calculated by the method of least squares and plotted against categories of age at menarche containing ≥1000 women. In addition, BMI at age 25 was plotted against age at menarche to look for differences in the association between age at menarche and BMI in early versus late adulthood. Associations with age at menopause were examined by similar methods. Means (95%CI) for SBP and DBP were further adjusted for BMI as a categorical variable in case of confounding.

SAS version 9.1, R version 2.7.2 and Microsoft Excel 2007 were used for analyses, graphing and tables respectively.

Figure 1. Location of 10 survey sites around China

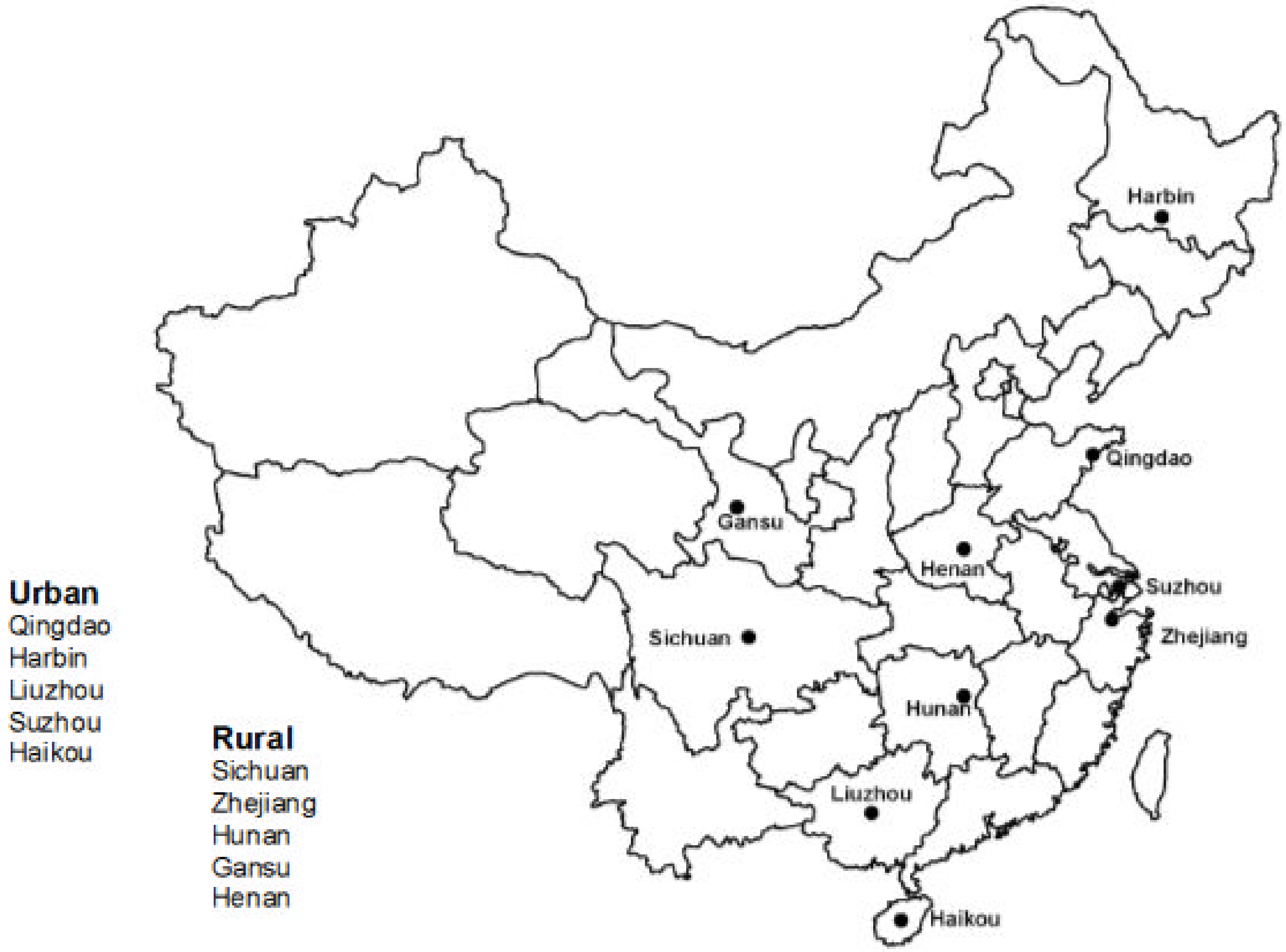


Table 1. Variables examined in this thesis

Category	Relevant questions	Major variables	Minor variables
Reproductive	9.1-9.10	- Age at menarche - Age at menopause, if applicable - Gravidity and parity: number of pregnancies, live births, still births, spontaneous abortions and induced abortions - History of OC use including duration of use, age at first use and age stopped if applicable - Age and duration of breastfeeding for each live birth	- Menopausal status - History of hysterectomy and age at time of procedure - History of oophorectomy and age at time of procedure - History of breast lumpectomy and age at time of procedure
Demographic	1.1-1.5	- Year of birth - Month and season of birth - Urban/rural residence - Area of residence	- Northern/southern residence - Coastal/inland residence
Socioeconomic	1.6-1.10	- Level of education - Occupation - Number of siblings - Annual household income	
Behavioural	3.1-3.4 and 4.1-4.5	- Frequency of soy consumption - History of smoking[1] - Smoking category - History of alcohol use[2] - Alcohol use category	
Physical	11.1-11.10	- Systolic blood pressure[3] - Diastolic blood pressure[3] - Height - Body mass index[4]	- Weight - Body fat percentage - Waist and hip circumference - Waist/hip ratio

[1] Only 'never smokers' (see Table 2) are considered to have no history of smoking and all other women are considered to have a history of smoking

[2] Only 'non-drinkers' (see Table 2) are considered to have no history of alcohol use and all other women are considered to have a history of alcohol use

[3] Mean of 2 readings taken consecutively at the baseline survey

[4] Calculated as weight divided by square of height, using measured weight and height at baseline survey

Table 2. Category definitions of demographic, socioeconomic and behavioural variables

Variable	Relevant questions	Categories (re-classified)	Response to questionnaire
Region	1.1-1.5	Northern	Harbin, Qingdao, Henan, Gansu and Suzhou
		Southern	Sichuan, Zhejiang, Hunan, Liuzhou and Haikou
		Coastal	Qingdao, Haikou, Zhejiang, Liuzhou and Suzhou
		Inland	Harbin, Hunan, Henan, Sichuan and Gansu
Education	1.6	No formal education	No formal school
		Primary school	Primary school
		Middle or high school	Middle school, High school
		Technical school or University	Technical school/college, University
Occupation	1.7	Manual	Agriculture, Factory worker
		Non-manual	Administrator, Professional, Sales/service workers
		Not currently working	Retired, Housewife, Unemployed
		Other	Self-employed, Other, Not stated
Alcohol use	3.1-3.4	Non-drinker	"Never or almost never drank alcohol in the past 12 months" AND "No period of drinking at least once a week in the past"
		Occasional drinker	"Drank only occasionally in the past 12 months" OR "Drank only at certain seasons in the past 12 months" AND "No period of drinking at least once a week in the past"
		Monthly drinker	"Drank every month" BUT "Drank less than weekly in the past 12 months" AND "No period of drinking at least once a week in the past"
		Current regular drinker	"Drank usually at least once a week in the past 12 months"
		Ex-regular drinker	EITHER "Never or almost never drank alcohol in the past 12 months" OR "Drank monthly, occasionally or only at certain seasons in the past 12 months" AND "Have a period lasting at least a year of drinking at least once a week in the past"
Smoking	4.1-4.5	Never-smoker	"Do not smoke now" AND "Did not smoke in the past" AND "Did not smoke today" AND "Have not smoked 100+ cigarettes in lifetime"
		Occasional smoker	("Do not smoke now" AND "Did not smoke in the past" BUT EITHER "Smoked today" OR "Have smoked 100+ cigarettes in lifetime"); OR ("Smoke occasionally now" AND "Never smoked" OR "Smoked occasionally in the past"); OR ("Smoked occasionally in the past" AND "Never smoke" OR "Smoke occasionally now")
		Current regular smoker	EITHER ("Smoked on most days/daily now" AND "Smoked on most days/daily in the past"); OR ("Smoked on most days/daily in the past AND "Smoked today" OR "Smoke occasionally now (i.e. not quit completely)"); OR ("Smoked on most days/daily in the past" AND "Did not smoke today" AND "Do not smoke now" AND "Stopped< 6 months ago (i.e. quit but for < 6months)")
		Ex-regular smoker	"Smoked on most days/daily in the past" AND "Do not smoke now" AND "Did not smoke today" AND "Stopped at least 6 months ago"

Chapter 5. Data Quality and Reproducibility

5.1 Results

5.1.1 Reproductive factors

A total of 12 003 women answered questions on reproductive history in the re-survey. All these women reported on age at menarche, age at menopause, number of pregnancies and OC use, but the number of women varied for other factors depending on responses to preceding questions – e.g. only a woman who responded ‘Yes’ to the question about OC use was asked about her age at starting OCs and the total duration of OC use. Table 1 and 2 show the level of agreement between baseline and re-survey reporting of reproductive variables using intra-class correlation coefficients (ICCs) and weighted kappas respectively. All reproductive variables were self-reported at baseline and re-survey.

Both age at menarche and age at menopause showed very good levels of agreement overall and by area. Age at menarche had an overall ICC of 0.83 (95% CI 0.82-0.85) that ranged from 0.70 to 0.87 between areas (Table 1). Similarly, age at menopause had an overall ICC of 0.78 (0.76-0.81) that ranged from 0.71 to 0.86 (Table 1). For both variables, urban women showed slightly better reproducibility (though the difference in ICCs was ≤0.04 for both: Table 1).

On the whole, OC use variables showed only moderate levels of agreement. Although the overall level of agreement for ever use of OCs was moderate (ICC of 0.57, 0.54-0.61: Table 1), it differed considerably between areas with ICCs ranging from 0.10 to 0.70

(Table 1). Reproducibility was quite poor in rural Hunan and urban Qingdao (ICCs of 0.41 and 0.43 respectively) and particularly poor in Haikou (ICC of 0.10: Table 1). Only 784 women (<7%) had data on age at starting OC use and duration of OC use at the re-survey with the number in each area ranging from 2 to 267 (Table 1). Areas with fewer than 100 women were greyed out in Table 1 to indicate that their ICCs were extremely unreliable. The overall ICCs were 0.64 (0.51-0.74) for age at starting OC use and 0.64 (0.52-0.74) for duration of OC use (Table 1), indicating reasonable levels of agreement when all women asked these questions were considered together.

Although gravidity showed very good agreement between the baseline and re-survey, the level of agreement for parity variables ranged from poor to good. Number of pregnancies showed a high level of agreement with an overall ICC of 0.90 (0.87-0.90) – ranging from 0.84 to 0.94 between areas – that was similar in both urban and rural women (Table 1). The level of agreement for number of live births was similarly good with an overall weighted kappa of 0.92 (0.90-0.93) that ranged from 0.84 to 0.98 between areas, although on average urban women showed better reproducibility than rural women (0.95 versus 0.89: Table 2). Number of induced abortions also had good reproducibility although it was slightly poorer than number of pregnancies or live births, with an overall weighted kappa of 0.64 (0.60-0.69). Urban women showed a higher level of agreement than rural women (0.71 versus 0.59) but the weighted kappas showed large variation between areas (0.30 to 0.76: Table 2). Number of still births and number of spontaneous abortions had the poorest reproducibility with overall weighted kappas of 0.37 (0.25-0.50) and 0.42 (0.33-0.52) respectively (Table 2). Reproducibility for these variables again differed between urban and rural women, with the average weighted kappa 0.10 higher for number of still births and 0.07 lower for number of spontaneous abortions in urban women (Table 2).

Number of still births and spontaneous abortions showed the largest variation between areas of any of the parity variables, with weighted kappas ranging from 0.17 to 0.75 and from 0.19 to 0.60 respectively (Table 2).

5.1.2 Physical characteristics

Physical measurements were taken at baseline and re-survey by trained field staff for 12 022 women from 10 areas. Weight at age 25 is the only physical characteristic that was self-reported at both baseline and re-survey. Table 3 shows the level of agreement between baseline and re-survey measurements using Spearman self-correlation coefficients. All physical measurements showed at the least a good level of agreement with some variables such as height showing near perfect agreement.

SBP and DBP showed good levels of agreement with overall self-correlations of 0.73 (0.72-0.74) and 0.66 (0.65-0.67) respectively. Self-correlations ranged among areas from 0.67 to 0.79 for SBP and 0.61 to 0.71 for DBP between areas.

Height, weight and BMI all showed near perfect levels of agreement with overall self-correlations of 0.99 (0.98-0.99), 0.94 (0.94-0.95) and 0.92 (0.92-0.93) respectively that ranged among areas from 0.97 to 0.99 for height, 0.93 to 0.96 for weight and 0.91 to 0.94 for BMI. Although BFP had a very good level of agreement, the overall self-correlation was lower than that for either BMI or weight at 0.84 (0.84-0.85) – ranging from 0.82 to 0.86. Self-correlations for weight at age 25 were even lower – 0.75 (0.74-0.75) overall, ranging from 0.58 to 0.79 – but still showed a good level of agreement.

WC and HC showed very good levels of agreement with overall self-correlations of 0.82 (0.81-0.82) and 0.79 (0.79-0.80) respectively that ranged between areas from 0.77 to 0.86 for WC and from 0.70 to 0.86 for HC. WHR showed the lowest agreement between baseline and re-survey with an overall self-correlation of 0.68 (0.67-0.69) and the greatest range among areas (from 0.58 to 0.80) of all the physical characteristics measured.

With respect to all physical characteristics, the level of agreement for urban and rural women was similar (difference between combined self-correlations ≤ 0.05), although urban areas showed slightly better reproducibility in most cases.

5.1.3 Famine exposure

All 12 022 women were asked about experiences of food shortage (rather than famine specifically) at both baseline and re-survey. Only women who reported having experienced food shortage in their lifetime were then asked about that year and associated weight loss and disease. Table 4 shows the level of agreement between baseline and re-survey reporting of famine exposure using ICCs.

Any exposure to food shortage was very poorly replicated with an overall ICC of 0.23 (0.18-0.28). ICCs ranged from -0.06 in Haikou to 0.54 in Zhejiang with only Gansu and Zhejiang having ICCs ≥ 0.50 (Table 4). Among those re-surveyed, only 1032 women reported ever being exposed to food shortage at both the baseline and re-survey. Consequently, only one urban and three rural areas had data on the year of worst food shortage, disease and weight loss for more than 100 women at both surveys. While it is not possible to comment on the level of agreement between the baseline and re-survey reporting of these variables in each area given the very small number of women, the low overall ICCs indicate poor reproducibility among all 1032 women with data.

5.2 Discussion

Age at menarche, age at menopause, number of pregnancies, number of live births, number of induced abortions and OC use showed very good reproducibility. Although small numbers of women re-surveyed on age at starting OC use and duration of OC use limited examination of reproducibility within most areas, these variables showed good reproducibility in the total re-surveyed population. By contrast, number of still births and number of spontaneous abortions showed poor reproducibility within all areas except Harbin and Hunan.

The overall high reliability of reproductive variables in CKB confirms the finding of a study of 1050 British women that there is no systematic under- or over-reporting of reproductive variables in older women [186]. Furthermore, a comparison of measured and reported reproductive history among 541 British women who participated in both the Million Women Study and the MRC National Survey of Health and Development found a high level of validity for reproductive variables recalled in middle age [162]. Thus it is possible that the reproductive variables reported by CKB women are valid and reliable, but corroboration with other medical records for these women is required to establish this. Although age at menopause appears to have been reliably reported by CKB women, the level of agreement was lower than that seen in the next largest study of 3756 Dutch women [48] but comparable or better than that seen in 3 smaller studies of 1473 American women [187], 565 Swedish [188] and 535 Portuguese women [189]. Similarly, the good reproducibility of age at menarche among CKB women was comparable to that seen in 3 small studies comprising 294 Italian [190], 477 Dutch [78] and 452 American women [191]. The degree of reproducibility for other reproductive variables was similar to that seen in European populations [189, 190], although the reliability of OC use and number of spontaneous abortions was notably better in the European populations [189, 190]. The difference in reliability of OC use may be due to earlier availability of OCs and a higher prevalence of OC use among European women – who showed good validity in reporting of OC use [149] – compared to CKB women. Problems with recalled number of spontaneous abortions and still births have also been described in 87 113 Norwegian women and may be related to the gestational age at the time of the abortion [192]. The distinction between a spontaneous abortion and a still birth is an artificial one based on gestational age or weight. Thus, it is possible that a woman may not recall the exact gestational age at the time of pregnancy loss or understand the difference between what is considered a spontaneous abortion versus a still birth on each occasion that she reports her parity, thereby leading to misclassification.

There was also good reproducibility of physical characteristics among the 12 022 women, with height, BMI and current weight showing very high levels of agreement between the baseline and re-survey data. Urban women generally showed slightly better reproducibility for all physical characteristics but the differences from rural women were small. Although self-correlations varied between areas, no single area had a self-correlation of <0.58 for any physical characteristic. These differences are possibly due in part to random measurement error or natural intra-individual variations as a result of, for example, diurnal or seasonal variation. The good reproducibility of weight at age 25 – the only self-reported physical characteristic – among CKB women, coupled with the finding by the Million Women Study that middle-aged women have accurate recall of body size at younger ages [162], indicates that this variable is a reasonable measure for comparison with current body size in this study.

Reporting of having ever been exposed to food shortage had poor reproducibility overall and in most areas, with only Gansu and Zhejiang showing reasonable levels of agreement. Regional differences in the reproducibility of the year of worst food shortage as well as associated disease and weight loss could not be examined as only very small numbers of women were re-surveyed on these variables within each area, but the overall reproducibility of these variables was similarly poor. The poor reproducibility of all famine exposure variables will have to be accounted for in any analyses of these variables.

Although most of the intra-person variability described in these variables is likely to be random, it does generally lead to a dilution of the estimate of the true association between exposure and outcome, and so must be accounted for in all subsequent analyses of this dataset [108] .

5.3 Conclusion

Among 12 022 women included in both the baseline and re-survey, physical characteristics showed very good reproducibility whereas reporting of exposure to food shortage was very poorly reproduced. Although the reproducibility of reproductive variables was generally good among 12 003 women with baseline and re-survey data, it varied from very good for age at menarche and menopause to very poor for number of spontaneous abortions and still births. Overall, CKB women showed similar reproducibility for reproductive and physical characteristics to that seen in European populations, although there were at times large regional variations. The effect of poor reproducibility – particularly for food shortage and some reproductive variables – will have to be accounted for in subsequent analyses.

Table 1. Level of agreement[1] between baseline and re-survey reporting of selected reproductive variables

Region	Age at menarche		Age at menopause		No. of pregnancies	
	No. of women	ICC	No. of women	ICC	No. of women	ICC
Harbin	1309	0.84 (0.83-0.86)	753	0.84 (0.82-0.86)	1309	0.91 (0.90-0.92)
Qingdao	909	0.86 (0.84-0.88)	588	0.86 (0.83-0.88)	909	0.87 (0.85-0.89)
Suzhou	1185	0.86 (0.85-0.88)	715	0.77 (0.74-0.80)	1185	0.91 (0.90-0.92)
Liuzhou	985	0.86 (0.84-0.87)	582	0.80 (0.77-0.83)	985	0.92 (0.91-0.93)
Haikou	691	0.80 (0.77-0.83)	349	0.71 (0.65-0.76)	691	0.87 (0.86-0.89)
Urban[2]	**5079**	**0.85 (0.83-0.86)**	**2987**	**0.81 (0.78-0.83)**	**5079**	**0.90 (0.89-0.91)**
Zhejiang	1459	0.87 (0.86-0.88)	801	0.81 (0.79-0.84)	1459	0.84 (0.83-0.86)
Hunan	1340	0.84 (0.82-0.85)	699	0.77 (0.73-0.79)	1340	0.94 (0.94-0.95)
Henan	1648	0.85 (0.84-0.86)	732	0.72 (0.68-0.75)	1648	0.85 (0.84-0.87)
Sichuan	1206	0.84 (0.82-0.85)	653	0.81 (0.78-0.83)	1206	0.86 (0.85-0.88)
Gansu	1271	0.70 (0.68-0.73)	552	0.72 (0.67-0.75)	1271	0.90 (0.88-0.91)
Rural[2]	**6924**	**0.82 (0.81-0.84)**	**3437**	**0.77 (0.73-0.80)**	**6924**	**0.88 (0.87-0.89)**
Overall[2]	**12003**	**0.83 (0.82-0.85)**	**6424**	**0.78 (0.76-0.81)**	**12003**	**0.89 (0.87-0.90)**

Region	OC use		Age started OC use		Duration of OC use	
	No. of women	ICC	No. of women	ICC	No. of women	ICC
Harbin	1309	0.69 (0.66-0.71)	91	0.58 (0.42-0.70)	91	0.71 (0.59-0.80)
Qingdao	909	0.43 (0.38-0.49)	20	0.79 (0.54-0.91)	20	0.66 (0.31-0.85)
Suzhou	1185	0.70 (0.67-0.73)	105	0.61 (0.47-0.72)	105	0.64 (0.51-0.74)
Liuzhou	985	0.70 (0.67-0.73)	162	0.63 (0.53-0.72)	162	0.70 (0.61-0.77)
Haikou	691	0.10 (0.03-0.18)	2	0.69 (-0.99-1.00)	2	-0.51 (-1.00-1.00)
Urban[2]	**5079**	**0.57 (0.53-0.61)**	**380**	**0.62 (0.48-0.73)**	**380**	**0.68 (0.55-0.77)**
Zhejiang	1459	0.69 (0.67-0.72)	267	0.69 (0.62-0.75)	267	0.74 (0.68-0.79)
Hunan	1340	0.41 (0.37-0.46)	34	0.59 (0.32-0.77)	34	0.93 (0.87-0.97)
Henan	1648	0.61 (0.58-0.64)	61	0.57 (0.38-0.72)	61	0.12 (-0.14-0.36)
Sichuan	1206	0.58 (0.54-0.62)	40	0.70 (0.49-0.83)	40	0.13 (-0.19-0.42)
Gansu	1271	0.57 (0.53-0.61)	2	0.96 (-0.95-1.00)	2	1.00 (0.00-0.00)
Rural[2]	**6924**	**0.58 (0.54-0.61)**	**404**	**0.66 (0.54-0.75)**	**404**	**0.60 (0.48-0.70)**
Overall[2]	**12003**	**0.57 (0.54-0.61)**	**784**	**0.64 (0.51-0.74)**	**784**	**0.64 (0.52-0.74)**

[1] Intra-class correlation coefficients

[2] Weighted average of area ICCs

Table 2. Level of agreement[1] between baseline and re-survey reporting of parity

Region	No. of women	No. of live births	No. of still births	No. of spontaneous abortions	No. of induced abortions
Harbin	1279	0.98 (0.97-0.99)	0.72 (0.63-0.81)	0.50 (0.38-0.62)	0.75 (0.72-0.78)
Qingdao	905	0.94 (0.91-0.96)	0.24 (0.01-0.47)	0.19 (0.07-0.30)	0.76 (0.73-0.79)
Suzhou	1174	0.93 (0.91-0.94)	0.41 (0.32-0.51)	0.37 (0.27-0.47)	0.72 (0.69-0.75)
Liuzhou	969	0.96 (0.95-0.97)	0.22 (-0.04-0.48)	0.45 (0.33-0.57)	0.67 (0.63-0.70)
Haikou	677	0.94 (0.93-0.96)	0.46 (0.30-0.62)	0.36 (0.24-0.49)	0.65 (0.60-0.69)
Urban[2]	**5004**	**0.95 (0.94-0.97)**	**0.43 (0.27-0.59)**	**0.38 (0.27-0.50)**	**0.71 (0.68-0.75)**
Zhejiang	1443	0.87 (0.85-0.89)	0.17 (0.09-0.26)	0.37 (0.28-0.47)	0.58 (0.55-0.62)
Hunan	1331	0.96 (0.95-0.97)	0.75 (0.70-0.79)	0.60 (0.54-0.67)	0.75 (0.72-0.79)
Henan	1635	0.87 (0.86-0.89)	0.17 (0.06-0.28)	0.35 (0.29-0.42)	0.62 (0.59-0.65)
Sichuan	1199	0.93 (0.92-0.95)	0.33 (0.20-0.45)	0.47 (0.38-0.57)	0.68 (0.65-0.72)
Gansu	1264	0.84 (0.82-0.86)	0.29 (0.15-0.43)	0.48 (0.42-0.55)	0.30 (0.16-0.44)
Rural[2]	**6872**	**0.89 (0.88-0.91)**	**0.33 (0.23-0.43)**	**0.45 (0.37-0.53)**	**0.59 (0.54-0.64)**
Overall[2]	**11876**	**0.92 (0.90-0.93)**	**0.37 (0.25-0.50)**	**0.42 (0.33-0.52)**	**0.64 (0.60-0.69)**

[1] Weighted kappas

[2] Weighted average of area kappas

Table 3. Level of agreement[1] between baseline and re-survey measurements of selected physical characteristics

Region	No. of women	SBP	DBP	Height	BMI	BFP
Harbin	1311	0.74 (0.71-0.76)	0.61 (0.57-0.64)	0.99 (0.99-0.99)	0.92 (0.92-0.93)	0.86 (0.84-0.87)
Qingdao	910	0.75 (0.71-0.77)	0.64 (0.60-0.68)	0.99 (0.98-0.99)	0.94 (0.93-0.94)	0.85 (0.83-0.87)
Suzhou	1185	0.71 (0.68-0.73)	0.66 (0.62-0.69)	0.99 (0.99-0.99)	0.93 (0.92-0.94)	0.85 (0.83-0.87)
Liuzhou	990	0.74 (0.71-0.76)	0.67 (0.63-0.70)	0.99 (0.99-0.99)	0.93 (0.92-0.94)	0.84 (0.82-0.86)
Haikou	694	0.79 (0.76-0.82)	0.71 (0.68-0.75)	0.99 (0.98-0.99)	0.94 (0.93-0.95)	0.86 (0.84-0.88)
Urban[2]	**5090**	**0.75 (0.71-0.76)**	**0.66 (0.64-0.67)**	**0.99 (0.99-0.99)**	**0.93 (0.93-0.94)**	**0.85 (0.85-0.86)**
Zhejiang	1459	0.68 (0.65-0.70)	0.63 (0.60-0.66)	0.98 (0.98-0.98)	0.93 (0.93-0.94)	0.82 (0.81-0.84)
Hunan	1342	0.73 (0.70-0.75)	0.64 (0.61-0.67)	0.98 (0.98-0.98)	0.93 (0.92-0.94)	0.86 (0.84-0.87)
Henan	1650	0.74 (0.72-0.76)	0.67 (0.64-0.70)	0.99 (0.98-0.99)	0.92 (0.91-0.93)	0.84 (0.83-0.86)
Sichuan	1210	0.67 (0.64-0.70)	0.64 (0.60-0.67)	0.99 (0.99-0.99)	0.91 (0.90-0.92)	0.84 (0.82-0.86)
Gansu	1271	0.71 (0.69-0.74)	0.62 (0.59-0.65)	0.97 (0.97-0.98)	0.92 (0.91-0.92)	0.84 (0.82-0.85)
Rural[2]	**6932**	**0.72 (0.70-0.73)**	**0.65 (0.64-0.66)**	**0.98 (0.98-0.98)**	**0.92 (0.91-0.92)**	**0.83 (0.83-0.84)**
Overall[2]	**12022**	**0.73 (0.72-0.74)**	**0.66 (0.65-0.67)**	**0.99 (0.98-0.99)**	**0.92 (0.92-0.93)**	**0.84 (0.84-0.85)**

Region	No. of women	Weight at baseline	Weight at age 25	WC	HC	WHR
Harbin	1311	0.93 (0.92-0.94)	0.77 (0.75-0.79)	0.86 (0.85-0.87)	0.80 (0.78-0.82)	0.73 (0.71-0.76)
Qingdao	910	0.95 (0.94-0.95)	0.67 (0.63-0.71)	0.86 (0.84-0.87)	0.81 (0.79-0.83)	0.74 (0.71-0.77)
Suzhou	1185	0.95 (0.94-0.95)	0.79 (0.76-0.81)	0.83 (0.82-0.85)	0.86 (0.84-0.87)	0.67 (0.64-0.70)
Liuzhou	990	0.94 (0.93-0.95)	0.76 (0.74-0.79)	0.80 (0.77-0.82)	0.79 (0.77-0.81)	0.71 (0.67-0.74)
Haikou	694	0.96 (0.95-0.96)	0.71 (0.67-0.75)	0.85 (0.82-0.87)	0.82 (0.80-0.85)	0.80 (0.77-0.82)
Urban[2]	**5090**	**0.94 (0.94-0.95)**	**0.76 (0.74-0.77)**	**0.83 (0.82-0.84)**	**0.82 (0.81-0.83)**	**0.71 (0.70-0.72)**
Zhejiang	1459	0.95 (0.94-0.95)	0.71 (0.68-0.73)	0.82 (0.80-0.84)	0.79 (0.77-0.81)	0.73 (0.70-0.75)
Hunan	1342	0.95 (0.95-0.96)	0.58 (0.52-0.63)	0.84 (0.82-0.85)	0.78 (0.76-0.80)	0.67 (0.64-0.70)
Henan	1650	0.94 (0.94-0.95)	0.76 (0.74-0.78)	0.79 (0.77-0.81)	0.78 (0.76-0.80)	0.58 (0.54-0.61)
Sichuan	1210	0.94 (0.93-0.94)	0.75 (0.72-0.78)	0.84 (0.82-0.85)	0.78 (0.76-0.80)	0.73 (0.70-0.76)
Gansu	1271	0.93 (0.93-0.94)	0.63 (0.57-0.69)	0.77 (0.75-0.79)	0.70 (0.67-0.73)	0.58 (0.54-0.62)
Rural[2]	**6932**	**0.94 (0.94-0.95)**	**0.72 (0.71-0.74)**	**0.81 (0.80-0.81)**	**0.77 (0.76-0.78)**	**0.66 (0.65-0.67)**
Overall[2]	**12022**	**0.94 (0.94-0.95)**	**0.75 (0.74-0.75)**	**0.82 (0.81-0.82)**	**0.79 (0.79-0.80)**	**0.68 (0.67-0.69)**

[1] Spearman self correlation coefficients

[2] Adjusted for area

Table 4. Level of agreement[1] between baseline and re-survey reporting of food shortage variables

Region	Ever exposed to food shortage		Year of worst food shortage		Weight loss associated with food shortage		Disease associated with food shortage	
	No. of women	ICC	No. of women	ICC	No. of women	ICC	No. of women	ICC
Harbin	1311	0.21 (0.16-0.26)	20	0.66 (0.32-0.85)	20	-0.26 (-0.63-0.20)	20	0.31 (-0.15-0.66)
Qingdao	910	-0.04 (-0.11-0.02)	19	1.00	19	-0.04 (-0.48-0.42)	19	0.25 (-0.23-0.63)
Suzhou	1185	0.31 (0.25-0.36)	190	0.40 (0.27-0.51)	190	-0.15 (-0.28-0.00)	190	0.16 (0.01-0.29)
Liuzhou	990	0.24 (0.18-0.30)	30	0.55 (0.23-0.76)	30	-0.38 (-0.03, -0.65)	30	0.31 (-0.05-0.61)
Haikou	694	-0.06 (-0.13-0.02)	0	-	0	-	0	-
Urban[2]	**5090**	**0.16 (0.10-0.22)**	**259**	**0.48 (0.25-0.53)**	**259**	**-0.17 (-0.37, 0.04)**	**259**	**0.19 (-0.02-0.38)**
Zhejiang	1459	0.54 (0.51-0.58)	430	0.19 (0.10-0.28)	430	-0.35 (-0.27, -0.43)	430	0.26 (0.17-0.34)
Hunan	1342	0.10 (0.05-0.15)	7	-0.12 (-0.78-0.67)	7	-0.47 (-0.89-0.40)	7	0.10 (-0.68-0.78)
Henan	1650	0.02 (-0.03-0.06)	42	-0.14 (-0.42-0.17)	42	-0.31 (-0.01, -0.56)	42	0.45 (0.17-0.66)
Sichuan	1210	0.33 (0.27-0.37)	120	0.74 (0.65-0.82)	120	0.08 (-0.10-0.25)	120	0.28 (0.10-0.43)
Gansu	1271	0.51 (0.47-0.55)	174	-0.21 (-0.06, -0.34)	174	-0.04 (-0.18-0.11)	174	0.21 (0.06-0.35)
Rural[2]	**6932**	**0.29 (0.24-0.33)**	**773**	**0.17 (0.05-0.28)**	**773**	**-0.21 (-0.34, -0.08)**	**773**	**0.26 (0.12-0.38)**
Overall[2]	**12022**	**0.23 (0.18-0.28)**	**1032**	**0.24 (0.10-0.35)**	**1032**	**-0.20 (-0.34, -0.05)**	**1032**	**0.24 (0.09-0.38)**

[1] Intra-class correlation coefficients

[2] Weighted average of area ICCs

Chapter 6. Baseline description of study population

6.1 Results

6.1.1 Demographic characteristics

A total of 302 180 women born 1930-74 from 10 areas were included in the baseline description. Figure 1 shows the distribution of year of birth and age at baseline among all women: there was a significant drop in the number of women born during the Great Chinese Famine[3] of 1958-61 – reflected in the number of women aged 44-48 – which was seen in all areas. Table 1 gives the distribution of selected demographic and behavioural characteristics overall and by urban or rural region and Figure 2 shows the proportion of women in selected demographic and behavioural categories by area and urban or rural region. The mean age at baseline survey was 51(SD 10.0) years and was similar in urban (52[11] years) and rural (50[10] years) women. Marital status showed a similar distribution in urban and rural women: 89% of all women were married, with slightly fewer in urban areas (86%) due mainly to slightly more widows and divorcées, and less

[3] The Great Chinese Famine (officially referred to as Three Years of Natural Disasters) occurred from 1958-1961. In late 1949, Mao Zedong declared the new People's Republic of China in Peking and formulated the first comprehensive five-year plan for economic growth. The projected industrial growth was made possible primarily through the extraction of a surplus from Chinese agriculture. The first programme involved partial land redistribution with private ownership mostly intact. The government then launched a second and more radical wave of land reform in order to capitalise further on agricultural production and prevent re-emergence of prior social patterns in rural areas. The second programme replaced this system with the merging of all agricultural land into large-scale cooperatives of around 200-300 households each. Almost all rural residents were enrolled in these cooperatives by the end of 1956. As the various reforms were not producing the same steady economic growth in the rural areas as in the urban centres, Mao decided a further risky initiative was needed and the cooperatives were further merged into massive communes under the title 'The Great Leap Forward'. This campaign had the goal of galvanizing human life and economy alike by removing entrenched distinctions of gender, age, skill and occupation but sadly ended in catastrophic widespread famine. The average amount of grain available to each person in China's countryside fell from 201kg to 154kg from 1958-1961 with 20 million people dying between 1959 and1962.

than 1% had never married (Table 1). The distribution of all other demographic characteristics differed between urban and rural women. Only 4% of all women had accessed tertiary education with a higher proportion of urban than rural women (9% versus 1%: Table 1). About half of all urban women had at least middle or high school education compared to approximately a quarter of all rural women (Table 1). However, even within urban and rural populations, the proportions varied considerably from 14 to 42% among rural areas and 30 to 82% among urban areas (Figure 2). More than half (58%: Table 1) of all women had at least 3 siblings with very little variation between areas (Figure 2). Just over half (51%) of all women worked in manual occupations and a third were not currently working (36%: Table 1). The proportion of rural women in manual occupations was about four-fold higher than urban women (76% versus 20%) but even among rural women there were differences between areas in the proportion of women in manual occupations (Figure 2). Conversely, the proportion of women in non-manual occupations was about 5 times higher in urban than in rural women (16% versus 3%: Table 1). About half (54%) the urban women had an annual household income ≥20 000 RMB compared with 30% of rural women, and only 4% of urban compared to 15% of rural women had an annual household income of <5000 RMB (Table1). Differences in household income were largest among rural areas, with the proportion of women with ≥20 000 RMB ranging from 2% in Gansu to 79% in Zhejiang (Figure 2).

Overall, the prevalence of smoking was very low in this population, with very little difference between urban and rural women. Only 5% of all women had ever smoked with 2% being current regular smokers (Table 1), although Harbin and Sichuan showed unusually high proportions of regular smokers (6% and 10% respectively: Figure 2). By contrast, 35% of all women currently drank alcohol, although the vast majority of these

(32%) only drank occasionally (Table 1). These patterns were similar between urban and rural women although Harbin and Sichuan again had unusually high proportions of regular drinkers (5% and 6% respectively: Figure 2).

6.1.2 Reproductive characteristics

Table 2 shows the distribution and unadjusted means of reproductive characteristics in this population overall and by urban and rural region. Mean age at menarche and menopause were similar between urban and rural populations. More than half (54%) of all women experienced menarche between ages 14 to 16 and only 3% had menarche either before age 11 or after 19, with unadjusted mean ages at menarche of 15[2.0] and 16[2.0] years for urban and rural women respectively. More than half (53%) of all women were postmenopausal – with a slightly higher proportion of urban women (55% versus 50%) – and the unadjusted mean age at menopause was 49[4.0] years among the 89 320 women included in the age at menopause analyses (i.e. aged ≥57 with natural menopause). OC use and menopause status showed similar patterns in urban and rural women. Only 10% of women had ever used OCs and less than 1% was currently using them.

Other reproductive factors showed different patterns between urban and rural women. More than 99% of all women had at least one live birth, but a greater proportion of urban women had only 1-2 live births (75% versus 60%). Overall, CKB women breastfed for an average of 15 [7.6] months, but urban women breastfed 4 months less on average than rural women (12 versus 16 months), which reflected that only 28% of urban women breastfed for more than 12 months compared with 59% of rural women. Just over half (52%) of all women had had at least one induced abortion, but more than two-thirds (68%)

of urban compared with 40% of rural women had experienced such an event. In contrast, although only 6% of the total population had ever had a spontaneous abortion, almost three times as many rural women had experienced a spontaneous abortion compared to urban women (8% versus 3%). Only 4% of the total population reported any previous gynaecological surgery with a higher proportion of urban women undergoing such procedures (9% versus <5%) and the most common procedure was a hysterectomy.

6.1.3 Physical characteristics

Table 3 shows the distribution and unadjusted means and Figures 3-4 show the age-related trends for selected physical characteristics measured at the baseline survey. The overall mean SBP/DBP was 130/77mmHg and was slightly lower in urban (127/76mmHg) than in rural women (132/78mmHg: Table 3). Just over a quarter (27%) of all women had an abnormally high SBP of ≥140mmHg at baseline, with slightly more rural women falling into this category (30% versus 24%: Table 3). SBP increased linearly with age in both urban and rural women by approximately 8.8 and 8.4mmHg per 10 years respectively (Figure 3a). By comparison, only 12% of all women had an abnormally high DBP of ≥90mmHg with again slightly more rural women falling into this category (13% versus 10%: Table 3). DBP also increased linearly with age by approximately 3.6 and 2.7mmHg per 10 years in urban and rural women respectively up to 55 years, after which it appeared to plateau or fall (Figure 3b). Although mean DBP was higher in rural women at all ages, the difference between urban and rural women attenuated from age 50.

Overall, CKB women were relatively short with a mean height of 154 [6.0] cm, although, on average, urban women were 2cm taller than rural women (155cm versus 153cm: Table

3). Height appeared to decrease linearly with age by approximately 2cm per 10 years in both urban and rural women (Figure 3c).

Two-thirds (66%) of CKB women had a BMI <25 – which is conventionally regarded as within a healthy range – with a slightly larger proportion of rural compared to urban women (70% versus 62%: Table 3). The age-related trends for BMI differed between urban and rural women (Figure 3d). For urban women, there was an increasing linear trend of 0.5kg/m^2 per 10 years older across the entire age range. By contrast, in rural women BMI increased with age to the same extent up to about age 50, but there was no similar trend among older women. As a consequence, the mean BMI was higher in urban than in rural women (24.3 kg/m^2 versus 23.5kg/m^2: Table 3).

Age-related trends of other anthropometric measures also differed between urban and rural women (Figure 4). Weight and HC showed similar patterns, increasing by approximately 2.5kg and 2.1cm per 10 years for both urban and rural women until about age 45, before plateauing in urban women and decreasing by approximately 2.5kg and 1cm per 10 years in older rural women (Figure 4a and 4d). As a result, the mean weight and mean HC for urban women were 4kg and 4cm higher than for rural women (59kg versus 55kg and 93cm versus 89cm: Table 3). BFP and WC showed similar patterns, with both increasing linearly with age by approximately 1% and 2.8cm per 10 years respectively throughout the age range among urban women (Figure 4b-c). Among rural women, however, BFP and WC increased by 1.5% and 4.5cm per 10 years respectively until age 45; thereafter, there was no trend for WC but BFP decreased by approximately 0.7% per 10 years. Consequently, mean BFP and mean WC were higher among urban than rural women (33% versus 32% and 80cm versus 78cm: Table 3). Due to the different trends in WC and HC for urban and rural women, the regional age-related trends for WHR converged (Figure 4e). Although a greater proportion of rural women had a WHR≥0.86 (57% versus 47%: Table 3), this reflected smaller hip circumferences rather than larger waist circumferences.

6.2 Discussion

6.2.1 Demographic characteristics

A total of 302 180 women born 1930-74 with a mean age of 51 years were included in the baseline description. Urban women were, on average, older, more highly educated and in a higher income group despite more than half not working at the time of baseline survey. Significant inter-regional variation was seen for education level, occupation and household income. Very few women smoked or drank and patterns of smoking and drinking were similar among both urban and rural women, with only Gansu and Sichuan showing unusually high proportions of both current regular smokers and drinkers.

The drop in the number of women born during the Great Chinese Famine reflects the severity of the famine, and may have been due to either a high prenatal mortality rate or a reduction in the number of conceptions. Women born during the Great Chinese Famine included in this study therefore represent the 'survivors' which might introduce a selection bias as analyses including these women concentrate on those that 'survived' the famine and unavoidably ignore those women that didn't. However, these women are only a small proportion of the total study population and therefore should not significantly bias analyses that include women from other year-of-birth cohorts.

Although almost all urban and rural women were either currently or formerly married, urban women were otherwise more highly educated, more likely to be employed in non-manual occupations and more highly paid. This may be due to more investment in infrastructure as well as greater access to education and higher-earning professional occupations among urban areas. However, these patterns were not always consistent among areas classified as either urban or rural, reflecting large heterogeneity in demographic variables across the areas included in this study. Furthermore, large differences in socioeconomic factors between urban and rural women may indicate differences in the level of exposure to other factors associated with socioeconomic status, such as nutrition.

Despite a generally increasing burden of chronic diseases and their known risk factors in China (see Introduction), the prevalence of either regular smoking or regular alcohol consumption was very low among CKB women. Despite an unusually high proportion of regular smokers and/or drinkers in Harbin and Sichuan, it was still below 10%. This may reduce confounding by smoking and alcohol consumption in analyses of all women included in this study, but should not limit the ability of this study to examine the effect of these exposures given the large absolute number of women who are regular smokers and drinkers.

6.2.2 Reproductive characteristics

Age at menarche, OC use and history of gynaecological surgery showed the same patterns among urban and rural women with more than half of women experiencing menarche at ages 14-16 and never having used OCs or undergone surgery. Rural women had, on average, a higher number of live births, longer average duration of breastfeeding and more spontaneous abortions, whereas urban women had more induced abortions. A slightly higher proportion of urban women was postmenopausal at the time of baseline survey and, among those women included in the age at menopause analyses, mean age at menopause was slightly higher in urban than rural women.

OC use was very low in both urban and rural women, probably because OCs only became available in China after the majority of CKB women no longer desired fertility (many may have chosen permanent contraception such as tubal ligation) or had entered menopause. However, the absolute number of women with a past history of OC use is sufficient to examine the effect of this exposure on age at menopause.

There were large differences in other reproductive factors between urban and rural areas that reflect regional variations in reproductive trends over the 20th century (see Introduction). Prior to the implementation of the One Child Policy, fertility rates were higher in rural areas, and although this rate dropped after the policy was introduced, it still did not approximate the urban rate during these women's reproductive lifetimes (see Introduction). This suggests that the national family planning programme was implemented later and/or less strictly enforced in the rural areas so that more rural women were able to exceed the one-child limit (and have a higher number of pregnancies with the potential to abort spontaneously). By comparison, stricter enforcement of family planning in urban areas may have resulted in higher numbers of those women who fell pregnant again after their first birth resorting to induced abortions to comply with regulations. Differences in duration of breastfeeding, however, are more likely due to differences in cultural practices as well as the greater availability of alternative feeding methods such as formula in urban areas. Although the differences in age at menarche and menopause between urban and rural areas were smaller than for other variables, analyses of these factors, as well as parity and breastfeeding, must be adjusted for area when trying to make comparisons between subgroups of the population.

6.2.3 Physical characteristics

Among those physical characteristics that showed the same trends among urban and rural women, SBP and DBP increased linearly with age and standing height decreased linearly with age. Among urban women, BMI, weight, BFP, WC, HC and WHR increased approximately linearly with age but plateaued after age 45 for weight and HC. Among rural women, these variables increased linearly with age until about age 45 after which they showed variables rates of decrease or no further trend. As a result, urban women, on average, had larger values for all anthropometric variables except WHR.

The age-related trends seen for SBP and DBP reflect increasing arterial stiffness at older ages and are consistent with those seen in several observational studies including the original Framingham Heart Study [193]. Differences in age-related changes in anthropometry between urban and rural women may be due to differences in the type and amount of food available, the preferred diet (e.g. traditional Chinese versus Western cuisine) and the proportion of people employed in physically strenuous jobs in each region, which has changed over time, particularly from the 1980s when China opened up to the Western world. Thus, age and region will need to be accounted for in subsequent analyses of blood pressure and anthropometry.

The decrease in adult standing height with increasing age seen in CKB women is due to a strong increasing secular trend in adult height rather than any age-related changes per se.

This may reflect long-term nutritional improvements at the population level and particularly better nutrition in childhood when chronic nutrition influences final adult height (see Literature Review: Age at menarche). The greater height seen in urban women at all ages suggests nutrition was persistently better in this region despite general improvements throughout China. Furthermore, there is no disruption of the secular trend in height for any year-of-birth cohort despite exposure to the Great Chinese Famine at different growth phases, which indicates no long-term effect of acute nutritional shortage on somatic growth.

Menopause-associated changes in the distribution of body fat have been noted previously [194]. The age-related trends in anthropometry seen among CKB women may reflect a similar change around the time of menopause but this association will be examined further in later analyses (see Chapter 9).

6.3 Conclusion

This large study population showed a wide range of demographic, physical and reproductive characteristics, making it a rich data source to examine any effect of the many different exposures measured on each other and on disease outcomes. In particular, there were large regional differences in socioeconomic factors, indicating that urban women generally had a higher socioeconomic status and were thus likely to have different levels of exposure to associated factors such as nutrition, as evident from regional differences in adult height. Important age-related trends in SBP and DBP as well as regional differences in anthropometry and reproductive factors need to be accounted for in later analyses. However, those reproductive factors that show large regional differences may be better examined separately for urban and rural women, particularly where the proportion of women in each exposure category is substantially different e.g. duration of breastfeeding and history of abortion. Survivor bias from inclusion of women born during the Great Chinese Famine, though important for famine exposure analyses, is unlikely to have a large effect on associations found in the total CKB population given the small proportion of women affected. The low prevalence of regular smoking, regular alcohol consumption and past or present OC use makes confounding by these factors less likely, but there are still sufficient numbers of women with these behaviours to permit reliable examination of these factors.

Table 1. Demographic and behavioural characteristics of study population

Characteristic	Urban (n=134 581) %	Rural (n=167 599) %	Overall (n=302 180) %
Age (years)			
30-39	13	18	16
40-49	30	31	31
50-59	31	31	31
60-69	19	15	17
≥ 70	7	4	5
Mean (SD)	*52 (11.0)*	*50 (10.0)*	*51 (10.0)*
Year of birth			
1930-1939	13	8	10
1940-1949	21	20	21
1950-1959	32	32	32
1960-1974	33	40	37
Mean (SD)	*1954 (11.0)*	*1956 (10.0)*	*1955 (10.0)*
Marital status			
Married	86	91	89
Widowed	11	8	9
Separated/divorced	3	<1	2
Never married	<1	<1	<1
Highest education			
No formal school	17	32	25
Primary School	20	40	31
Middle or High School	53	27	39
Technical school / college or University	9	1	4
Number of siblings			
0	3	3	3
1 to 2	27	26	27
3 to 4	58	58	58
5-7	11	11	11
>7	2	2	2
Occupation			
Manual	20	76	51
Non-manual	16	3	9
Not currently working	57	19	36
Other	6	2	4
Annual household income (RMB)			
<5000	4	15	10
5000-19 999	42	55	49
≥20 000	54	30	41
Smoking history			
Never smoker	96	94	95
Occasional smoker	2	2	2
Ex-regular smoker	1	1	1
Current regular smoker	2	3	2
Alcohol history			
Non-drinker	62	65	64
Current regular drinker	2	2	2
Occasional drinker	34	31	32
Monthly drinker	2	1	1
Ex-regular drinker	1	1	1

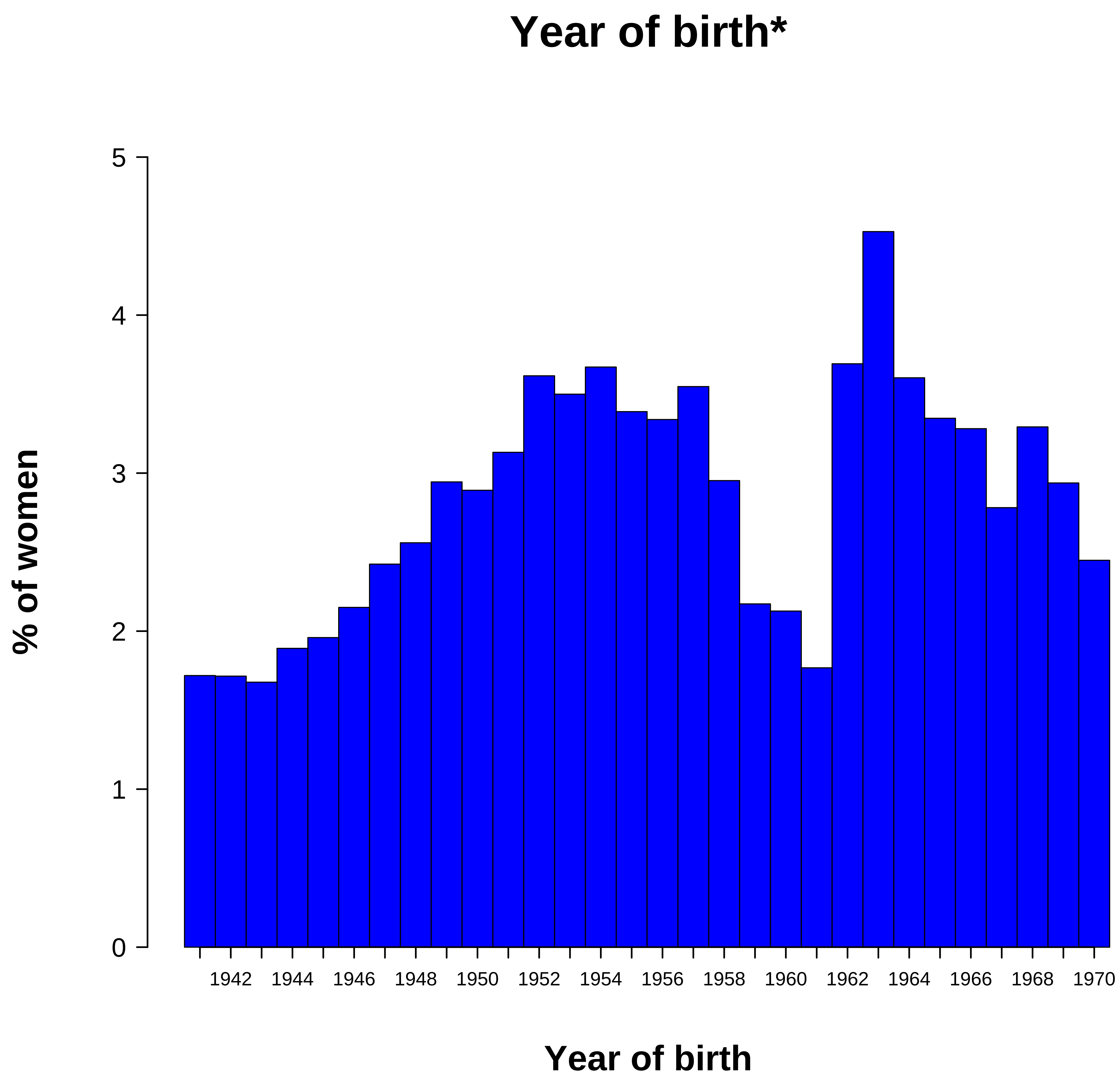
Table 2. Reproductive characteristics of study population

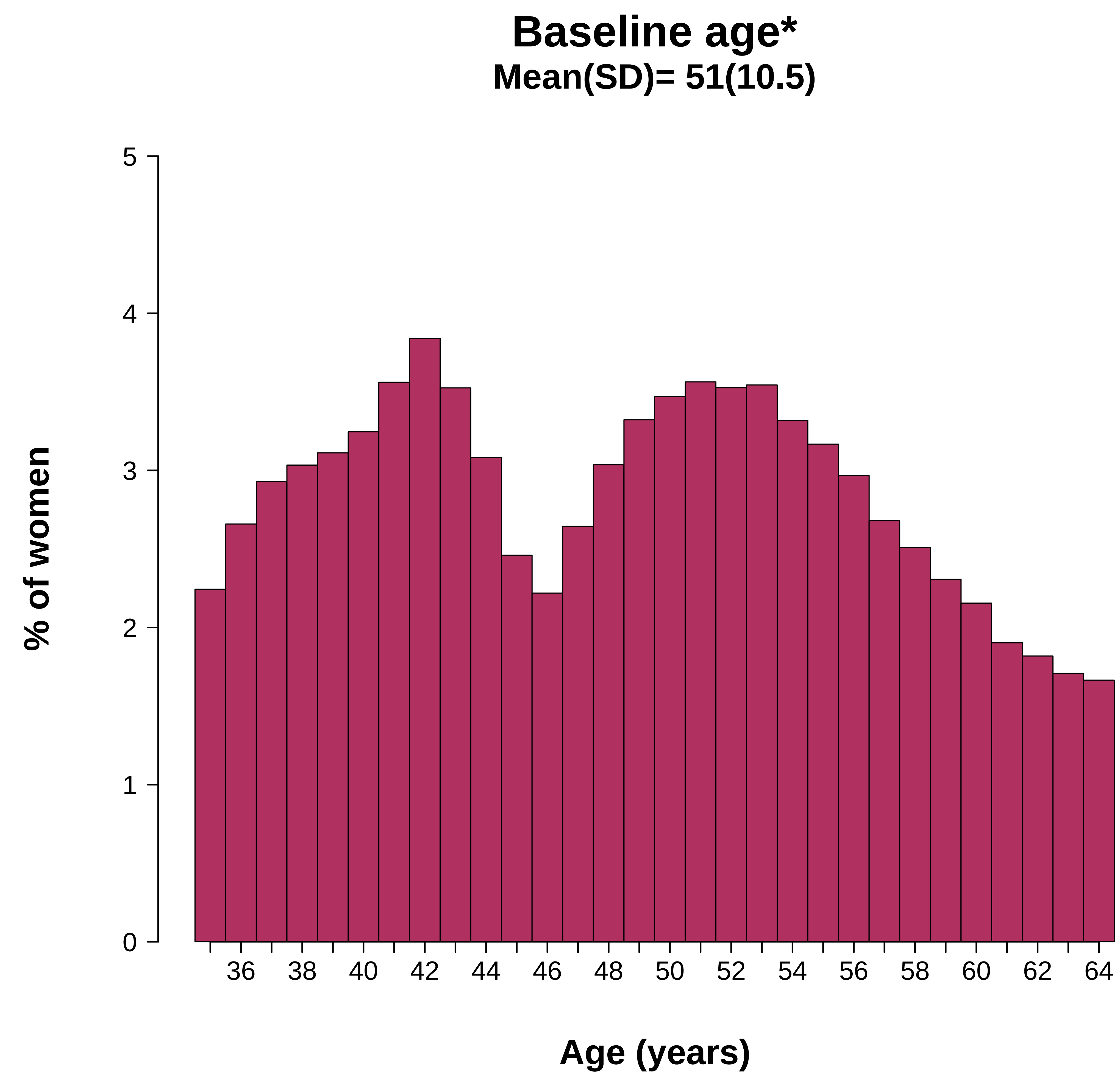
Characteristic	Urban (n=134 581) %	Rural (n=167 599) %	Overall (n=302 180) %
Age at menarche			
<11	<1	<1	<1
11-13	20	15	17
14-16	53	55	54
17-19	25	28	27
>19	2	2	2
Mean (SD)	*15 (2.0)*	*16 (2.0)*	*15 (2.0)*
OC use			
Never used	89	91	90
Past use	11	8	10
Current use	<1	<1	<1
Number of live births			
0	1	<1	<1
1 to 2	75	60	67
3 to 5	23	36	30
>5	1	4	3
Average length of breastfeeding (months)	(n=131 985)	(n=166 115)	(n=298 100)
No breastfeeding	4	1	3
≤ 6	9	4	6
7-12	59	36	46
13-18	18	28	23
19-24	7	21	15
>24	3	10	7
Mean (SD)	*12 (6.4)*	*16 (8.0)*	*15 (7.6)*
History of abortion			
No history of abortion	29	52	42
History of spontaneous abortion	3	8	6
History of induced abortion	68	40	52
Gynaecological surgery			
Hysterectomy	5	3	4
Oophorectomy	2	1	2
Breast lumpectomy	2	<1	1
Menopausal status			
Pre-menopausal	39	45	43
Peri-menopausal	5	5	5
Post-menopausal	55	50	53
Age at menopause	(n=44 669)	(n=44 651)	(n= 89 320)
<45	12	16	14
45-46	12	12	12
47-48	18	19	18
49-50	24	23	23
51-52	15	15	15
>52	18	16	17
Mean (SD)	*49 (4.0)*	*48 (5.0)*	*49 (4.0)*

Table 3. Physical characteristics of study population

Characteristic	Urban (n=134 581) %	Rural (n=167 599) %	Overall (n=302 180) %
SBP (mmHg)			
<110	21	13	17
110-124	30	29	30
125-139	24	28	26
140-155	13	15	14
≥155	11	15	13
Mean (SD)	*127 (21.7)*	*132 (22.0)*	*130 (22.0)*
DBP (mmHg)			
<60	5	3	4
60-69	25	20	22
70-79	37	36	36
80-89	23	27	25
≥90	10	13	12
Mean (SD)	*76 (10.7)*	*78 (11.0)*	*77 (10.9)*
Standing height (cm)			
<150	18	28	24
150-154	30	33	31
155-159	31	27	28
≥160	22	12	17
Mean (SD)	*155 (5.9)*	*153 (5.9)*	*154 (6.0)*
Weight (kg)			
<45	7	14	11
45-49	10	15	13
50-54	17	21	19
55-59	20	19	19
≥60	46	31	38
Mean (SD)	*59 (9.5)*	*55 (9.2)*	*57 (9.5)*
BMI(kg/m²)			
<20	10	15	12
20-24	52	55	54
25-29	32	26	29
≥30	6	4	5
Mean (SD)	*24.3 (3.5)*	*23.5 (3.4)*	*23.8 (3.5)*
% body fat			
<25	12	18	15
25-29	23	25	24
30-34	29	26	28
35-39	21	18	19
≥40	14	12	13
Mean (SD)	*32.7 (6.9)*	*31.6 (7.2)*	*32.1 (7.1)*
Waist circumference (cm)			
<70	14	19	17
70-79	37	40	39
80-89	34	30	31
≥90	15	12	13
Mean (SD)	*80 (9.5)*	*78 (9.5)*	*79 (9.5)*
Hip circumference (cm)			
<85	10	24	18
85-89	21	31	27
90-94	31	27	29
≥95	38	18	27
Mean (SD)	*93 (7.0)*	*89 (6.3)*	*91 (6.9)*
Waist/hip ratio			
<0.82	31	22	26
0.82-0.86	22	21	21
≥0.86	47	57	52
Mean (SD)	*0.86 (0.07)*	*0.87 (0.07)*	*0.87 (0.07)*

Figure 1. Proportion of women by year−of−birth and baseline age





*Only values with >5000 women are shown

Figure 2. Variation of selected baseline variables across 10 study areas

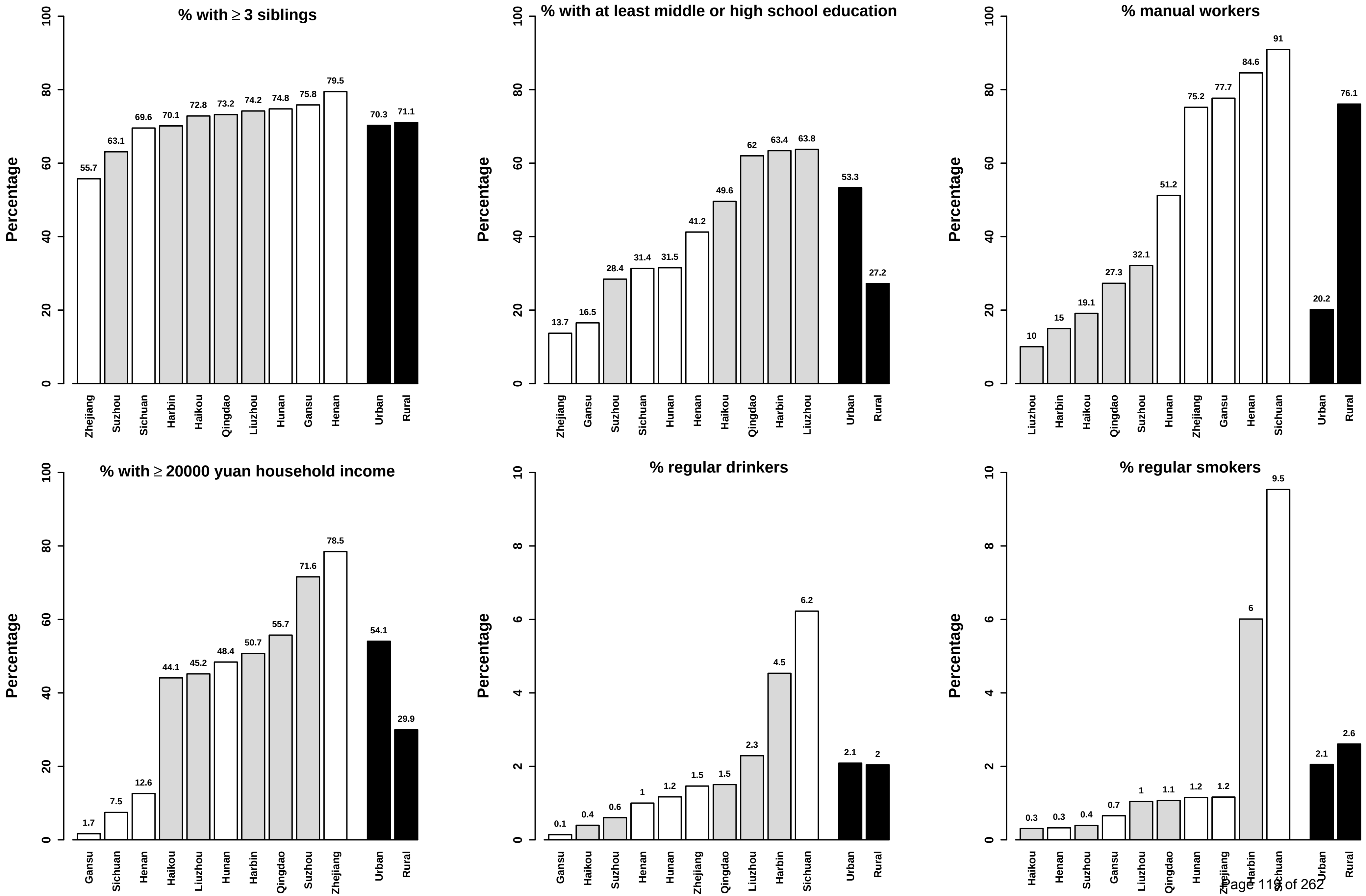
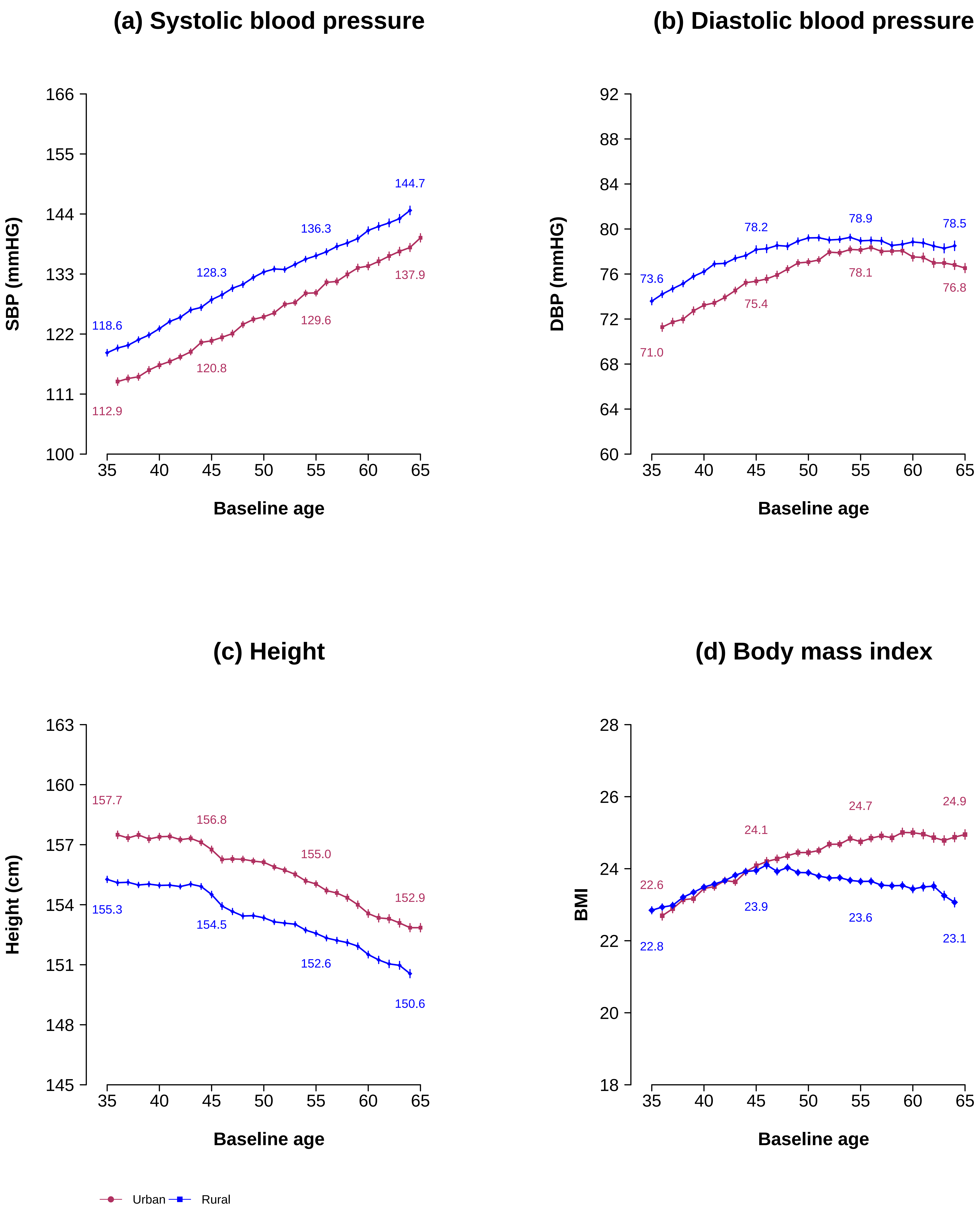


Figure 3. Age−related trends* of selected physical characteristics in urban and rural women

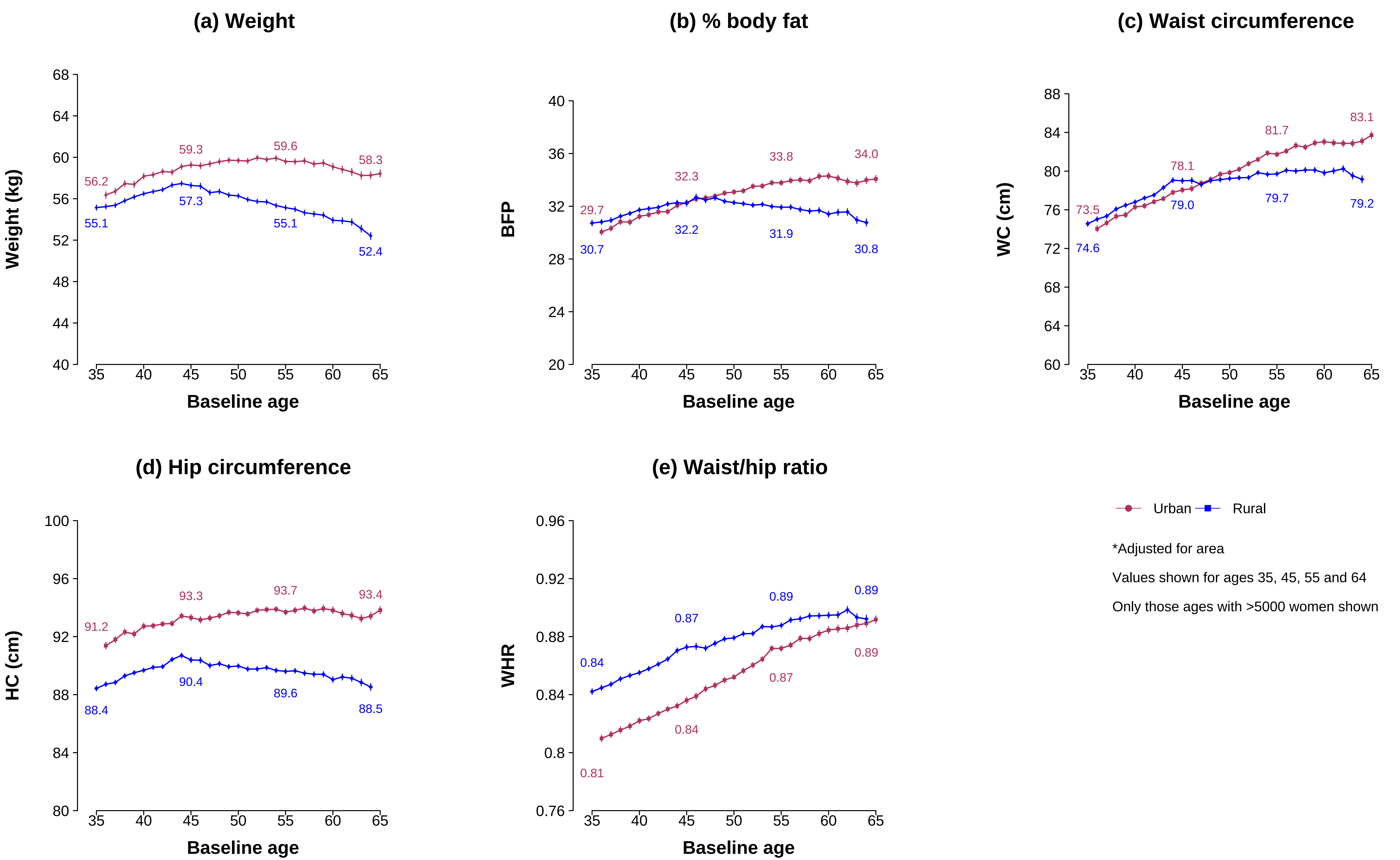


*Adjusted for area

Values shown for ages 35, 45, 55 and 64

Only those ages with >5000 women shown

Figure 4. Age−related trends* of selected anthropometric measurements in urban and rural women



Chapter 7. Age at menarche: regional variation, secular trend and main correlates

7.1 Results

7.1.1 Regional and socioeconomic variation in age at menarche

A total of 302 180 women from 10 areas born in 1930-74 were included in these analyses, of whom 55% were from rural areas. Figure 1 shows the distribution of age at menarche and Table 1 shows the mean age at menarche by area, region and year of birth. There was a normal distribution of age at menarche both overall (Figure 1a) and in urban and rural regions separately (Figure 1b). The overall mean age at menarche was 15.4 [SD 2.0] years and approximately 90% of all women experienced menarche in the age range 13-18 years (Figure 1a). The adjusted mean age at menarche was 0.32 years higher in rural than in urban women (15.59 versus 15.26 years, $p<0.0001$: Table 1), although it varied greatly between areas, more so in urban areas. Among urban areas, the adjusted mean age at menarche ranged from 14.65 years in Liuzhou to 15.78 years in Qingdao ($\chi^2_{(4)} = 8194$, $p<0.0001$); and among rural areas, it ranged from 15.38 years in Zhejiang to 15.74 years in Sichuan ($\chi^2_{(4)} = 677$, $p<0.0001$: Table 1). The adjusted mean age at menarche was 0.08 years (i.e. 1 month) higher in northern compared to southern regions and 0.13 years higher in inland compared to coastal regions ($p<0.0001$ for both: Table 1).

Table 2 shows the relationship of age at menarche with education, current occupation and number of siblings as measures of childhood SES. All these factors showed highly statistically significant associations with age at menarche, but the trend with education was by far the strongest. There was an inverse association of age at menarche with education, with the mean age at menarche decreasing by 1.10 years from 15.84 years in women with no formal education to 14.74 years in women with tertiary education (Trend $\chi_{(1)}^2 = 6585$, $p<0.0001$). There were significant differences in mean age at menarche among the 4 occupation categories, ranging from 15.57 years in women in manual occupations to 15.23 years in women in non-manual occupations ($\chi^2_{(3)} = 1234$, $p<0.0001$). Number of siblings showed a weaker trend than education: mean age at menarche increased with number of siblings from 15.12 years in women with no siblings up to 15.52 in women with 5-7 siblings (Trend $\chi_{(1)}^2 = 443$, $p<0.0001$). No significant changes to the results were seen when each socioeconomic factor was adjusted for the others.

7.1.2 Secular trends of mean age at menarche, early menarche and late menarche

Figure 2 shows the secular trend for the area-adjusted mean age at menarche across 44 year-of-birth cohorts both overall (Figure 2a) and by area (Figure 2b). Overall, mean age at menarche decreased by 2.0 years over 44 years from 16.2 years for women born in 1930 to 14.2 years for women born in 1974 (Figure 2a). Although the downward trend was predominantly linear, there was an anomalous period of increase in mean age at menarche for women born from 1940 (15.9 years) to 1945 (16.6 years) after which the downward secular trend resumed with mean age at menarche reaching 16.0 years again for women born in 1950. These women, born in 1940-50, were aged 8-18 at the approximate start of the Great Chinese Famine in 1958 that affected all regions of China to a greater or lesser extent [195]. This pattern of an overall decreasing secular trend with a deviation for women born in 1940-50 was seen in all 10 areas (Figure 2b). However, the overall decrease in mean age at menarche varied between areas (Table 1), from 0.6 years in Gansu to 2.9 years in Qingdao (Figure 2b), as did the exact timing and steepness of the deviation from the downward trend (Figure 2b).

Figure 3a shows the secular trend of the area-adjusted mean age at menarche for urban and rural regions separately. Although rural women born before 1940 had lower mean ages at menarche in each year than urban women, the deviation in the secular trend began earlier among rural women, starting with women born in 1937, peaking at 16.7 years among women born in 1944-5, and only returning to the pre-deviation mean of 15.9 years among women born in 1954. This pattern was mirrored to a lesser extent among urban women born 1940-50, peaking at 16.5 years for women born in 1946 but returning to the pre-deviation mean more quickly, so that women born in 1950 had returned to the same mean of 15.8 years as women born in 1940. Therefore the deviation from the secular trend affected 10 year-of-birth cohorts in urban women compared to 17 year-of-birth cohorts in rural women. Although the downward secular trend for rural women born after 1955 paralleled that of urban women, rural women had a higher mean age at menarche for all subsequent year-of-birth cohorts. As a result, urban women experienced a greater overall decrease in mean age at menarche compared to rural women (2.0 versus 1.8 years: Figure 3a).

Figure 3b shows the secular trend in mean age at menarche stratified by the highest education level attained across 44 year-of-birth cohorts. As seen in Table 2, mean age at menarche decreased with increasing level of education in every year-of-birth cohort and, although the downward trend was similar across all education levels, the deviation became less pronounced with increasing level of education (Figure 3b).

Figure 4 shows the secular trend in the area-adjusted prevalence of early (< 13 years) and late (>18 years) menarche. Late and early menarche were defined as being more than plus or minus 2.5 years (respectively) away from the mean age at menarche for the whole population (see Literature Review: Age at menarche [180]). As expected, the adjusted prevalence of late menarche showed a similar secular trend to that for mean age at menarche, decreasing from 10.7% among women born in 1930 to 0.8% among women born in 1974. An anomalous period of increase was seen for women born in 1939-50 that peaked at 16.9% for women born in 1944 who were aged 14 at the start of the Great Chinese Famine. Conversely, the adjusted prevalence of early menarche increased from 1.5% among women born in 1930 to 11.6% among women born in 1974. In this case, an anomalous period of decrease was seen for women born 1943-52 that had a nadir of 1.8% for women born in 1947 who were aged 11 at the start of the Great Chinese Famine. These changes reflect a constant distribution around a shifting mean age at menarche, with the deviation in the secular trend of late menarche (which affected women aged 8-19 in 1958) more pronounced than the deviation in the secular trend of early menarche (which affected women aged 6-15 in 1958).

7.1.3 Famine exposure and age at menarche

Table 3 shows the relationship between age at menarche and various aspects of famine exposure. Overall, famine exposure was associated with significant delays in age at menarche, with those women ever exposed to famine experiencing menarche 0.12 years later than women who had never been exposed ($p<0.0001$). Moreover, among women ever exposed, the difference was greatest if the exposure occurred prior to menarche rather than after it (0.98 years, p<0.0001). More severe premenarcheal famine exposure was associated with a further delay in menarche, as seen in women who reported either disease or weight loss in conjunction with premenarcheal famine exposure (0.16 years) or who reported premenarcheal famine exposure in 1955-64 around the time of the Great Chinese Famine (0.21 years, p<0.0001 for both).

To explore the effect of education on the association of age at menarche with famine exposure, mean age at menarche versus timing of famine exposure was stratified by highest education level attained in Table 4. There were clear age differences in exposure groups at all education levels which reflect these women's ages at the time of the Great Chinese Famine: unexposed women were on average the youngest (although there were women from all year-of-birth cohorts in this category) whereas women exposed to famine after menarche were on average older than those exposed before menarche. The proportion of women exposed to famine decreased steadily with increasing level of education from 39% of women with no formal education to 17% of women with primary education and 4-5% of women with secondary or tertiary education. However, the delay in menarche among women exposed before versus after menarche showed a U-shaped association with education, so that women with no schooling or tertiary education had a difference of 0.84 years compared to 1.12 and 1.17 years among women with primary and secondary education respectively (p<0.0001 for all).

7.1.4 Adult standing height, month and season of birth and age at menarche

Figure 5 shows the adjusted mean age at menarche plotted against adult standing height. There was only a very weak association between height and mean age at menarche among all women (Figure 5a) or in any of 4 birth cohort groups (Figure 5b). Overall, age at menarche increased by 0.8 months per 10 cm increase in standing height ($p<0.0001$) which is a very small effect despite being highly statistically significant. Birth cohorts paralleled each other and, with the exception of the 1940-49 cohort, women in older birth cohorts experienced menarche later (Figure 5b). Notably, the 1940-49 cohort – who were exposed to the Great Chinese Famine in late childhood and early adolescence – had the highest mean age at menarche in each height range. By contrast, famine exposure appeared to have no effect on the mean height of any year-of-birth cohort as seen in its steadily increasing secular trend (see Baseline Description: Results).

Table 5 shows the adjusted mean age at menarche by season of birth overall and for urban and rural regions. Overall, mean age at menarche was lowest for women born in spring (15.30 years) and highest for women born in autumn (15.57 years) – a difference of 0.27 years (i.e. 3 months), that was similar in both urban and rural regions ($p<0.0001$ for all), despite rural women experiencing menarche later for all seasons of birth.

To investigate this trend further, mean age at menarche was plotted against month of birth in Figure 6. Overall, mean age at menarche was lowest for women born in February (15.2 years) and highest for women born in December (15.6 years) – a difference of 0.4 years (approximately 5 months) (Figure 6a). Again, however, rural women had a higher mean age at menarche for all months of birth (Figure 6b). Surprisingly, both the highest and lowest mean ages at menarche by month of birth were during winter, indicating that the greatest fall in mean age at menarche occurs over 2 months during this season.

7.2 Discussion

In this extremely large cohort of over 300 000 women born in 1930-74, the overall mean age at menarche was 15.4 years, with about 90% of women having menarche between 13 and 18 years of age. However, there were large variations in mean age at menarche by area, year of birth and SES. Overall, there was a 2 year decrease in mean age at menarche across the 44 year-of-birth cohorts. Although the decreasing trend was predominantly linear, there was an anomalous period of rapid increase for women born between 1940 and 1950, who were aged 8-18 at the start of the Great Chinese Famine. This pattern was seen in all areas, but the anomaly was less pronounced among urban and more highly-educated women.

There was a significant delay of about a year in mean age at menarche among women who reported ever experiencing famine prior to menarche. A further delay in mean age at menarche was seen if the famine was with associated disease or weight loss or if maximal exposure occurred during the Great Chinese Famine. Moreover, women with better childhood SES (e.g. higher education or fewer siblings) were found not only to have a significantly lower mean age at menarche, but also to have been relatively protected against famine exposure. Education and ever being exposed to premenarcheal famine were the only factors associated with more than 6 months difference in mean age at menarche between women in the highest and lowest exposure categories. Another interesting finding was the sinusoidal association between mean age at menarche and month of birth, with those born in February having the lowest and those born in December having the highest age at menarche; surprisingly, both the highest and lowest ages at menarche occur during winter.

7.2.1 Secular trends, regional and socioeconomic variation and the prevalence of early and late menarche

As in other populations, age at menarche showed a normal distribution with 90% of women falling into a 5-year range [70-72]. Although the overall mean age at menarche was higher in this study than the current mean in developed countries [74, 85, 88, 89, 91-93], it may be comparable to other populations born around the mid-20th century.

Age at menarche has shown a decreasing secular trend in most populations over the 20th century (see Literature Review: Age at menarche). Similarly, age at menarche decreased continuously over the last few decades in CKB women, with the exception of a short period of anomalous increase among women who were in early adolescence during the Great Chinese Famine. The pace and degree of change in age at menarche in China were greater than that seen in most other populations [25, 86, 87, 89, 90, 93, 98], probably due chiefly to rapid improvement in nutrition at the population level in the latter half of the 20th century. The restriction of the anomaly to those women exposed to famine in late childhood or early adolescence – with no effect on women born during or just after the same period – is consistent with the findings of other studies of 745 Chuvashian [93, 100], 21 767 Dutch [78, 101], 21 000 Japanese [98] and 286 205 European women [34] , all of whom were exposed to famine as a result of WWII.

In the present study, women from poorer rural areas had menarche 0.3 years later than their urban counterparts, which is smaller than the 0.6 years difference between regions observed in 5736 Nigerian women [111]. A major strength of this study is the diversity in demographic characteristics across 10 areas. As a consequence, the large variation in mean age at menarche seen across different areas in this study is probably more extreme than that in other studies. Moreover, there also appeared to be differences both in the rate of long-term decline across different study areas as well as in the magnitude of the deviation from the secular trend, possibly reflecting both differences in long-term nutritional changes at the population level and the extent of exposure to famine. In particular, the rate of decline was steeper and the deviation less pronounced in urban women, suggesting that this population experienced greater long-term improvements in nutrition and was relatively protected against famine exposure.

There is a large body of evidence on the association of age at menarche with childhood SES that has consistently shown an earlier age at menarche with better childhood SES, regardless of the measure of SES being used (see Literature Review: Age at menarche). In this study, age at menarche was delayed among women with indicators of lower childhood SES, with education having the greatest effect. Compared to other studies, the difference in mean age at menarche between women with the highest and lowest indicators was more than twice as large for education [109, 110], only half as large for occupation [25, 111] and comparable for number of siblings [25, 77, 111]. Although these associations were not significantly changed by adjustment for each other, they are not likely to be causal, rather reflecting the effect of other environmental exposures such as nutrition on age at menarche. This is supported by the decreasing impact of famine with increasing level of education seen in the secular trend, where the delay in menarche due to famine exposure began later and was less pronounced among more highly educated women. More educated women were also relatively protected against ever being exposed to famine. The stronger trend with education seen in this study may be due to much larger differences in SES between the least and most educated women and/or greater variation in level of education compared to the two smaller studies of this association in 8030 Norwegian [110] and 2644 Ghanaian women [109] i.e. residual confounding. This greater variation in SES with education may be partly attributed to restriction of migration between urban and rural areas in China under Mao's system of household registration called *hukou,* with the result that rural women were denied access to benefits of urban residence including compulsory education and a greater variety in food [196].

There are limitations to measuring childhood SES in a cross-sectional study of adults. Other studies have used parental occupation as a measure of childhood SES [25, 111] but as that information was not available, each participant's own occupation was used in this study: another consequence of *hukou* was little or no movement between occupational sectors [196]. Following the economic reforms of the 1980s, social mobility became possible across China but entry into and movement between work sectors has remained reliant on *guanxi* networks [197] (interpersonal connections that carry a sense of obligation towards another [198]) which are still stronger in urban communities and favour men [196]. Despite probably minimal migration between occupation groups by CKB women, adult occupation is still only a weak surrogate for childhood SES. Hence, although it is unlikely that the differences in mean age at menarche between the CKB occupation categories are due to chance given the large sample size, these results should still be interpreted with caution.

The secular trends in prevalence of early and late menarche were expected given the pattern of the secular trend in the mean age at menarche. The difference in age range of the women affected by the deviations is a statistical artefact of the women's ages when the famine struck. Changes in the prevalence of early menarche could only be seen in those women aged under 13 years at the time of famine exposure (by definition), and so excludes women born prior to 1943 if 1958 is regarded as the approximate start of famine exposure. By contrast, famine exposure could potentially cause late menarche among all women who had not yet experienced menarche at the time of exposure, as it has no upper age limit.

7.2.2 Nutrition and age at menarche

Several studies in countries affected by post-WWII famine or food restrictions have consistently found that famine exposure is associated with approximately a year delay in age at menarche and has even slowed or temporarily reversed secular trends (see Literature Review: Age at menarche). The delay in menarche of 0.98 years among CKB women with famine exposure prior to versus after menarche was similar in magnitude to that in other populations but changed in magnitude with level of education, partly reflecting the severity of famine exposure. Although cross-sectional data cannot be used to establish the causal relationships, it is possible to gauge the time of famine exposure in relation to menarche among the women in this study using year of birth, self-reported age at menarche and the officially documented timeline of the Great Chinese Famine. That the deviation in the secular trend of age at menarche coincided with when women undergoing puberty were exposed to the Great Chinese Famine supports the finding of an effect of famine exposure on age at menarche at the population level.

The evidence on the association of age at menarche with self-reported and geographical classification of severity of famine exposure comes predominantly from cross-sectional analyses of 21 067 Dutch women exposed to famine post-WWII. Among the Dutch women, there was no significant association between geographical classification of severity of famine exposure and risk of experiencing late menarche, even though self-reported severity of famine exposure in a given year was associated with lower risk of experiencing menarche in that year [78]. By contrast, this study found differences in mean age at menarche by area and level of education, which can be partly explained at least by the extent of famine in each area (as urban women are on average more highly educated than rural women). This was corroborated by significant associations between mean age at menarche and self-reporting of the severity of famine exposure. The discrepancy in study findings on geographical classification of severity of famine exposure may be due to smaller variation in the extent of famine exposure between areas in Holland – a much smaller country with less geographical and socioeconomic diversity – compared with the areas in CKB. In both studies, self-reporting may have captured differences in severity of individual famine exposure better than geographical classification. There is potential misclassification of exposure with self-reporting but, provided it is random, such measurement error would attenuate any associations towards the null. In this study, given the relatively poor reproducibility in reporting of famine exposure (see Data Quality: Results), its real association with age at menarche is likely to be much greater.

There is limited evidence on the association of adult height with age at menarche, but weak positive correlations have been reported in a few studies of 2254 American, 288 985 European (from 9 countries) and 995 Bangladeshi women [34, 91, 105, 106] (see Literature Review: Age at menarche). In this study, adult standing height was used as a weak proxy for long-term childhood nutritional status [103, 104] (as more specific data were not available) and showed a very weak but significant association with age at menarche that was far smaller in magnitude to previous studies. There is very little variation in height among CKB women, with 90% of all women having an adult standing height in the range of 142-166cm (see Baseline Description: Results). Genes account for the majority of the variation in individuals' heights [97] with a much smaller role played by childhood nutrition. It is possible that the relatively small variation in height among CKB women may limit the ability of this study to examine the association of age at menarche with the smaller component attributable to childhood nutrition, despite the large sample size.

Although adult height has been used as a proxy for long-term childhood nutritional status in another smaller study of childhood correlates of age at menarche in Chinese women [199] – and may be considered a reasonable proxy among CKB women given that short-term famine exposure had no long-term impact on height among survivors at the population level (see Baseline Description: Results) – there are limitations to this approach. Firstly, adult height can only show whether nutrition throughout childhood was consistently poor enough or whether acute nutritional insults were sustained and severe enough to produce stunting. Secondly, it is impossible to establish cause and effect as early menarche can cause growth plates to fuse earlier resulting in a shorter adult height. Thirdly, the association between age at menarche and adult height may be confounded by childhood weight and diet (see Literature Review: Age at menarche). None of these issues can be addressed by this cross-sectional study of adult women; thus, the contrast between the association of age at menarche with long-term childhood nutritional status and famine exposure among CKB women must be interpreted with caution.

7.2.3 Month or season of birth and age at menarche

Only a few small studies have examined the association of age at menarche with either month or season of birth, with inconsistent results: only one cross-sectional study of 2992 American women found that women born in October-December had a significantly lower mean age at menarche than those born during either January-March or April-June but not July-September [114]. In this study, a sinusoidal trend was seen with both the highest and lowest mean ages at menarche occurring during the winter season. The reason for this association is not clear, and further information on other environmental exposures that may vary with month of birth is required to clarify the mechanism. The differences between study findings may be due to the much larger number of women in CKB providing sufficient power to detect this weak sinusoidal trend. Furthermore, if this study's results are real, then grouping month of birth as in the American study may have hidden the full extent of a trend seen more clearly with finer exposure categories.

7.3 Conclusion

Among CKB women, mean age at menarche has decreased by approximately 2 years over 44 year-of-birth cohorts: a greater rate than seen in other populations, probably due to relatively greater improvements in nutrition at the population level. Despite this trend, famine exposure was associated with a delay in menarche among women experiencing puberty around the time of the Great Chinese Famine, although the effect size varied among study areas. This pattern has also been seen in other populations exposed to famine following WWII, with the anomaly restricted to those women entering puberty as in CKB. Education has had a dual effect on age at menarche, with more educated women experiencing menarche earlier and being relatively protected against the effect of famine exposure. This is partly due to better-educated women generally having a higher SES possibly leading to better nutrition in childhood, although there was only a very weak association between age at menarche and long-term childhood nutrition, as represented by adult height. There was a sinusoidal association between month of birth and age at menarche for reasons not fully understood.

Due to its large size and detailed demographic data, this study offers far greater insight on the secular trend of age at menarche in China over the last century, as well as its association with famine, socioeconomic factors and month of birth than has previously been possible. The findings from this study may well be relevant to other South-East Asian populations and developing countries.

Table 1. Mean age at menarche by 5 year birth cohort and region

Area	No of women	1930-34	1935-39	1940-44	1945-49	1950-54	1955-59	1960-64	1965-69	1970-74	All year-of-birth groups (95% CI)[1]	Test statistic
		Year of birth										
Urban (Name of city)												
Harbin	34079	15.53	15.54	15.47	15.70	15.08	14.98	14.71	14.26	13.84	14.96 (14.94-14.98)	
Qingdao	19878	16.82	16.67	16.62	17.04	16.19	15.70	15.06	14.67	14.38	15.78 (15.76-15.81)	
Suzhou	30891	16.38	16.06	16.48	16.72	16.01	15.60	15.04	14.56	14.21	15.62 (15.60-15.64)	
Liuzhou	30835	15.59	15.47	15.41	15.51	14.77	14.43	14.24	13.92	13.75	14.65 (14.62-14.67)	
Haikou	18898	17.10	16.64	16.36	16.33	15.82	15.50	15.22	14.86	14.45	15.69 (15.67-15.72)	**$\chi^2_{(4)}$=8194 (p<0.0001)[2]**
Rural (Name of province)												
Zhejiang	33676	16.06	15.98	16.31	16.16	15.58	15.31	14.97	14.62	14.00	15.38 (15.36-15.40)	
Hunan	33516	15.69	15.74	16.40	16.42	15.95	15.71	15.29	14.78	14.46	15.62 (15.60-15.64)	
Henan	35510	16.01	15.77	16.39	16.54	16.02	15.65	15.11	14.59	14.18	15.58 (15.56-15.60)	
Sichuan	34342	16.10	16.04	16.60	16.76	16.24	15.81	15.28	14.66	14.18	15.74 (15.72-15.76)	
Gansu	30555	15.74	15.81	16.23	16.27	15.88	15.66	15.27	14.86	14.57	15.63 (15.61-15.65)	**$\chi^2_{(4)}$=677 (p<0.0001)[2]**
												$\chi^2_{(9)}$=11205 (p<0.0001)[2]
Region												
Urban	134581	16.15	15.93	15.94	16.18	15.46	15.17	14.81	14.43	14.15	15.26 (15.25-15.27)	
Rural	167599	15.94	15.87	16.40	16.43	15.94	15.62	15.18	14.70	14.38	15.59 (15.58-15.60)	
Difference											**0.32 (0.31-0.34)**	**z=47 (p<0.0001)**
Northernmost 5	150913	16.02	15.89	16.14	16.43	15.80	15.50	15.04	14.61	14.30	15.48 (15.47-15.49)	
Southernmost 5	151267	16.10	15.92	16.20	16.22	15.66	15.32	15.00	14.59	14.27	15.41 (15.40-15.42)	
Difference											**0.08 (0.06-0.09)**	**z=11 (p<0.0001)**
Coastal 5	168257	16.31	16.08	16.17	16.28	15.58	15.25	14.88	14.51	14.27	15.37 (15.36-15.38)	
Inland 5	133923	15.78	15.74	16.17	16.36	15.85	15.55	15.13	14.66	14.30	15.50 (15.49-15.51)	
Difference											**0.13 (0.11-0.14)**	**z=18 (p<0.0001)**
All regions	**302 180**	**16.12**	**15.96**	**16.20**	**16.33**	**15.74**	**15.42**	**15.01**	**14.55**	**14.19**	**15.44 (15.44-15.45)**	**$\chi^2_{(Trend)}$=36373 (p<0.0001)**

[1]Adjusted for year of birth

[2]Test for heterogeneity

Table 2. Mean age at menarche versus socioeconomic factors

Socioeconomic factor	No of women (n= 302 180)	Mean[1] age at menarche (95% CI)		Test statistic
Education level				
No formal school	76393	15.84	(15.82-15.85)	
Primary School	94997	15.57	(15.56-15.59)	
Middle or High School	117407	15.16	(15.15-15.17)	
Technical school or University	13383	14.74	(14.71-14.77)	$\chi^2_{(Trend)}$=6585 (p<0.0001)
Difference[2]		**1.10**	**(1.06-1.14)**	
Current occupation				
Manual	154666	15.57	(15.56-15.58)	
Non-manual	27013	15.23	(15.21-15.25)	
Not currently working	109232	15.31	(15.30-15.33)	
Other	11269	15.51	(15.48-15.55)	$\chi^2_{(3)}$=1234 (p<0.0001)[3]
Number of siblings				
0	7655	15.12	(15.08-15.16)	
1 to 2	80435	15.33	(15.32-15.35)	
3 to 5	174257	15.49	(15.49-15.50)	
5 to 7	33845	15.52	(15.50-15.54)	
>7	5614	15.39	(15.34-15.43)	$\chi^2_{(Trend)}$=443 (p<0.0001)
No. missing	374			
Difference[2]		**0.26**	**(0.20-0.33)**	

[1]Adjusted for area and year of birth
[2]Difference between top and bottom categories
[3]Test for heterogeneity

Table 3. Mean age at menarche versus exposure to famine

Type of famine exposure	No of women	Mean[1] age at menarche (95% CI)	Test statistic
Exposed to famine during lifetime (n= 302 180)			
No	249646	15.42 (15.42-15.43)	
Yes	52534	15.54 (15.52-15.56)	
Difference		**0.12 (0.10-0.14)**	**z=12 (p<0.0001)**
Period of famine exposure before menarche (n=52 534)			
No	17561	14.87 (14.84-14.90)	
Yes	34973	15.85 (15.83-15.87)	
Difference		**0.98 (0.94-1.02)**	**z=50 (p<0.0001)**
Exposed before menarche with either disease or weight loss (n=34 973)			
No	20467	15.78 (15.76-15.81)	
Yes	14506	15.94 (15.91-15.97)	
Difference		**0.16 (0.12-0.20)**	**z=8 (p<0.0001)**
Exposed before menarche during Great Chinese Famine (n=34 973)			
No	1190	15.65 (15.54-15.75)	
Yes[2]	33783	15.86 (15.84-15.88)	
Difference		**0.21 (0.12-0.31)**	**z=4 (p<0.0001)**

[1]Adjusted for area and year of birth

[2]The Great Chinese Famine occurred from ~1958-1961 but famine exposure reported 1955-64 is included in this group

Table 4. Mean age at menarche versus famine exposure by education level

Period of famine exposure	No of women (n=302 180)	Proportion of women[1] (%)	Mean year of birth	Mean[2] age at menarche (95% CI)	Test statistic
No formal school					
Not exposed	46745	61	1951	15.81 (15.79-15.83)	
After menarche	11834	16	1937	15.32 (15.28-15.36)	
Before menarche	17814	23	1949	16.16 (16.13-16.19)	
Difference[3]				**0.84 (0.80-0.88)**	**z=35 (p<0.0001)**
Primary school					
Not exposed	78581	83	1955	15.56 (15.55-15.57)	
After menarche	4103	4	1939	14.85 (14.79-14.91)	
Before menarche	12313	13	1949	15.98 (15.94-16.01)	
Difference[3]				**1.12 (1.06-1.18)**	**z=33 (p<0.0001)**
Middle or High school					
Not exposed	111478	95	1959	15.16 (15.15-15.18)	
After menarche	1408	1	1940	14.36 (14.26-14.46)	
Before menarche	4521	4	1950	15.53 (15.48-15.59)	
Difference[3]				**1.17 (1.05-1.29)**	**z=21 (p<0.0001)**
Technical school or University					
Not exposed	12842	96	1960	14.74 (14.70-14.77)	
After menarche	216	2	1940	14.21 (13.96-14.45)	
Before menarche	325	2	1950	15.04 (14.85-15.24)	
Difference[3]				**0.84 (0.78-0.90)**	**z=5 (p<0.0001)**

[1]Within each education level

[2]Adjusted for area and year of birth

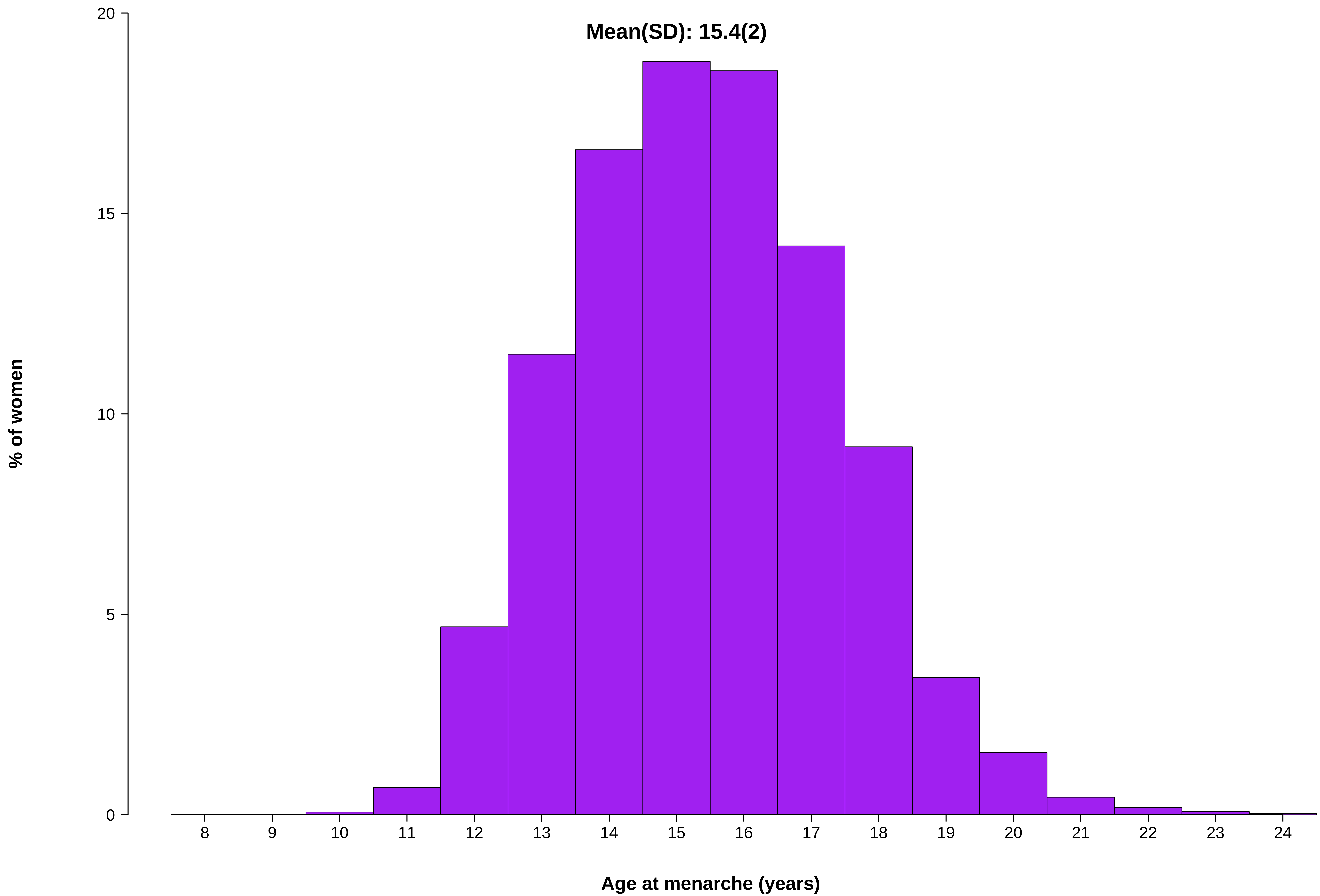
[3]Difference between women exposed before versus after menarche

Table 5. Mean age at menarche by season of birth

	Urban (n= 134 581)			Rural (n= 167 599)			Overall (n=302 180)		
Season of birth	No of women	Mean[1] age at menarche (95% CI)	Test statistic	No of women	Mean[1] age at menarche (95% CI)	Test statistic	No of women	Mean[1] age at menarche (95% CI)	Test statistic
Winter[2]	33006	15.28 (15.26-15.30)		41806	15.55 (15.53-15.56)		74812	15.43 (15.41-15.44)	
Spring[3]	30668	15.18 (15.16-15.20)		39328	15.40 (15.38-15.42)		69996	15.30 (15.29-15.31)	
Summer[4]	32758	15.32 (15.30-15.34)		40820	15.55 (15.53-15.57)		73578	15.45 (15.43-15.46)	
Autumn[5]	38149	15.44 (15.42-15.46)		45645	15.68 (15.67-15.70)		83794	15.57 (15.56-15.59)	
Difference[6]		**0.26 (0.24-0.28)**	**z=19 (p<0.0001)**		**0.28 (0.26-0.30)**	**z=23 (p<0.0001)**		**0.27 (0.25-0.29)**	**z=29 (p<0.0001)**

[1]Adjusted for area and year of birth
[2] Winter: Dec-Feb
[3] Spring: Mar-May
[4] Summer: June-Aug
[5] Autumn: Sept-Nov
[6]Difference between Spring and Autumn

Figure 1a. Proportion of women by age at menarche



Note: Only women with age at menarche in range 8−24 years shown

Figure 1b. Proportion of women by age at menarche in urban and rural women

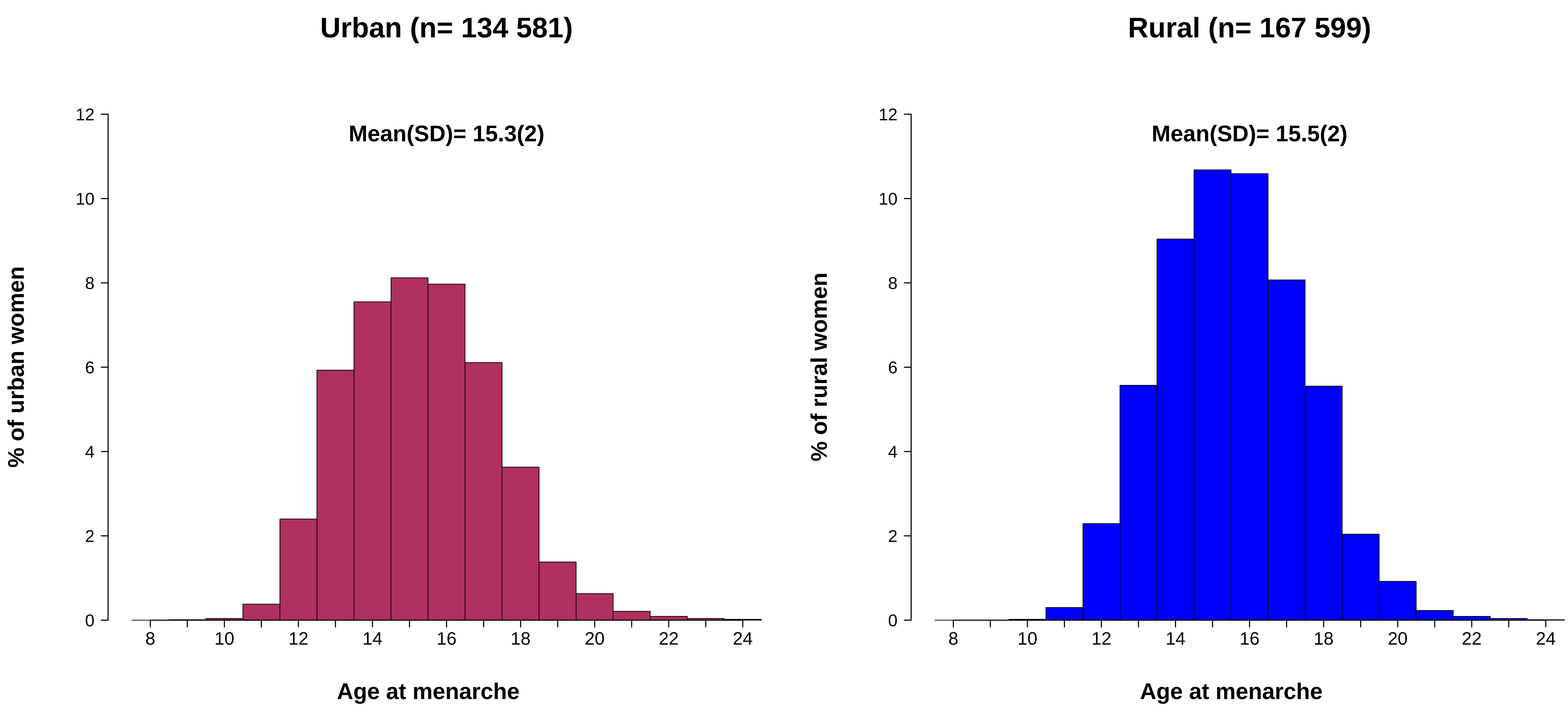
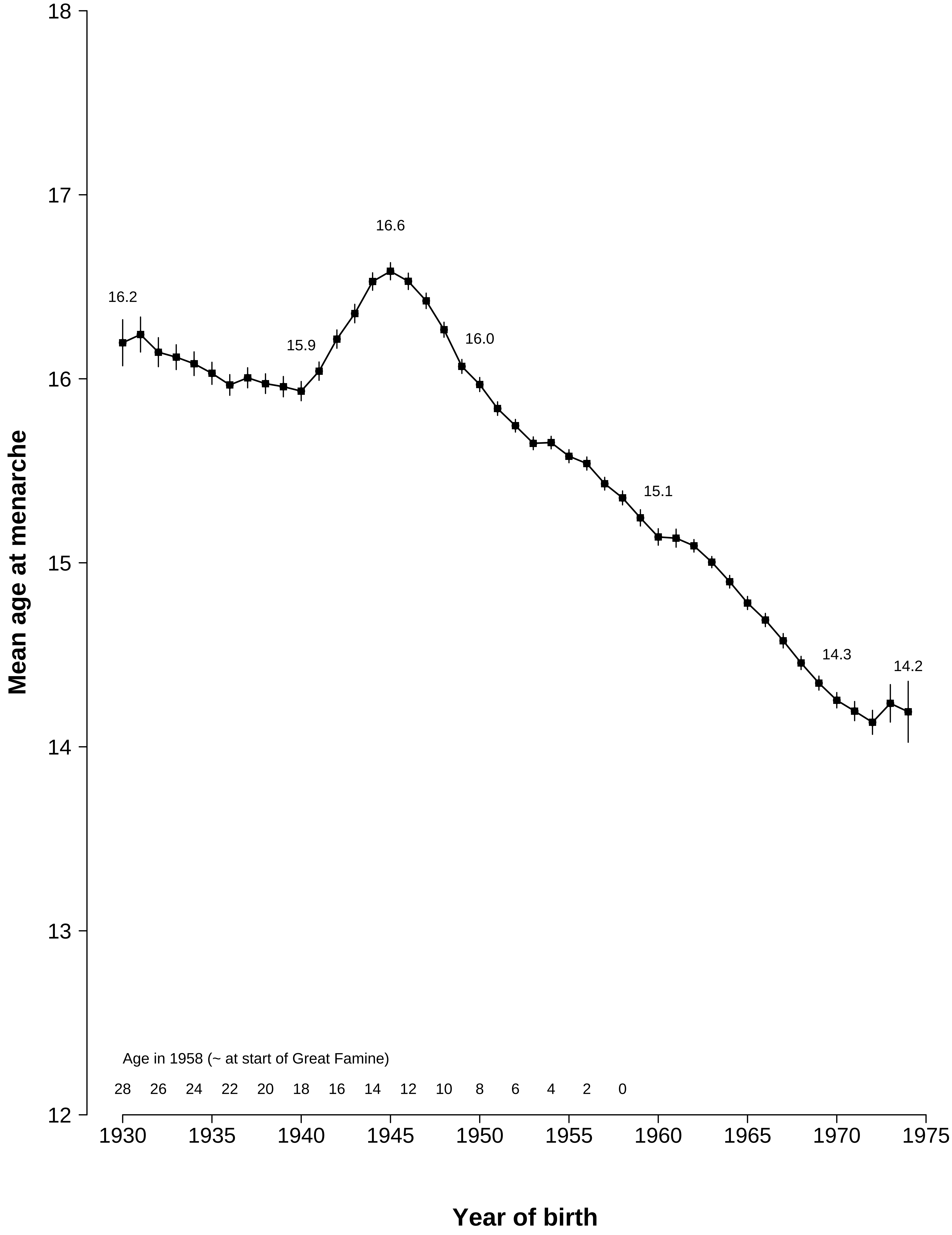
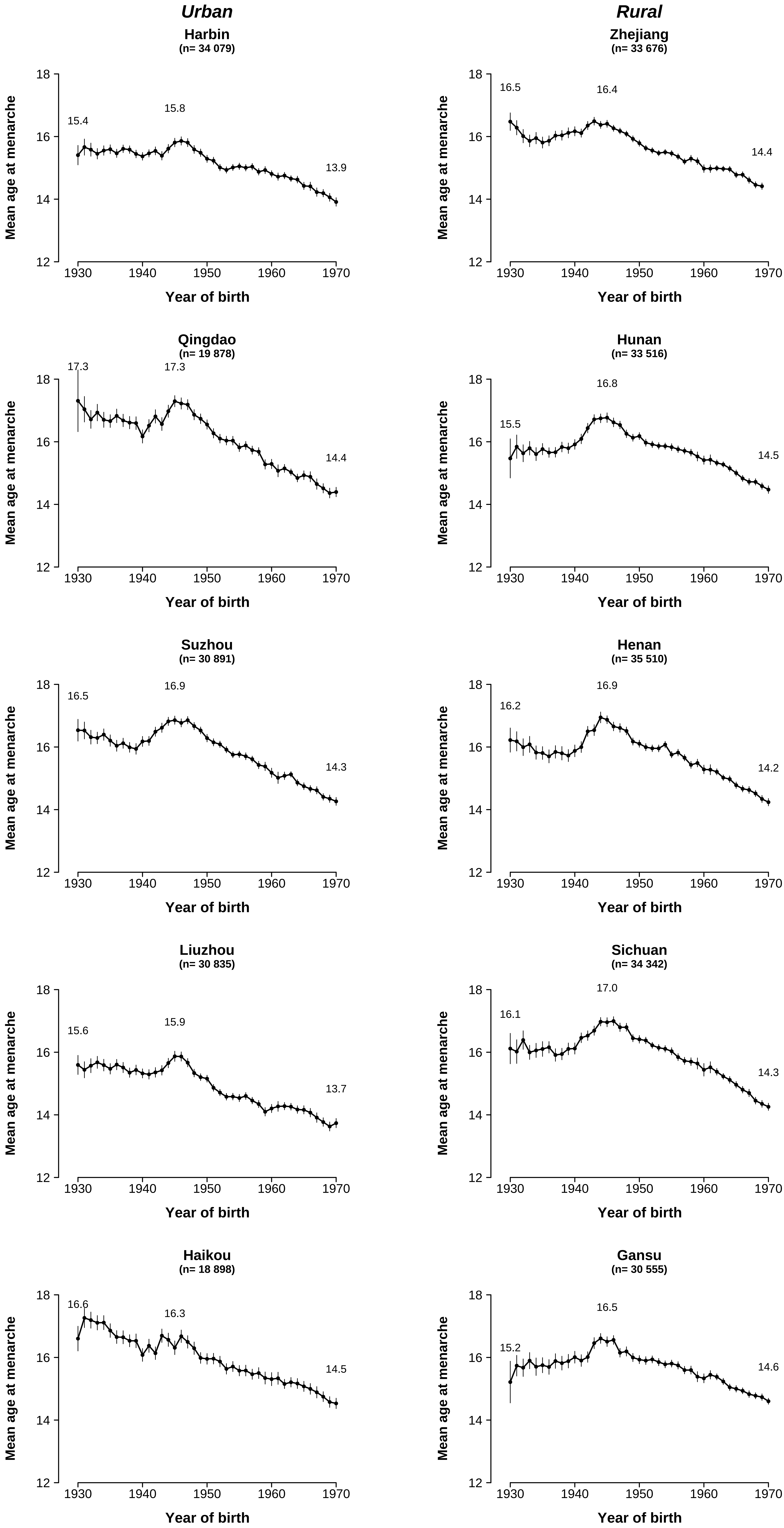


Figure 2a. Area−adjusted mean age at menarche by year of birth in 302 180 women



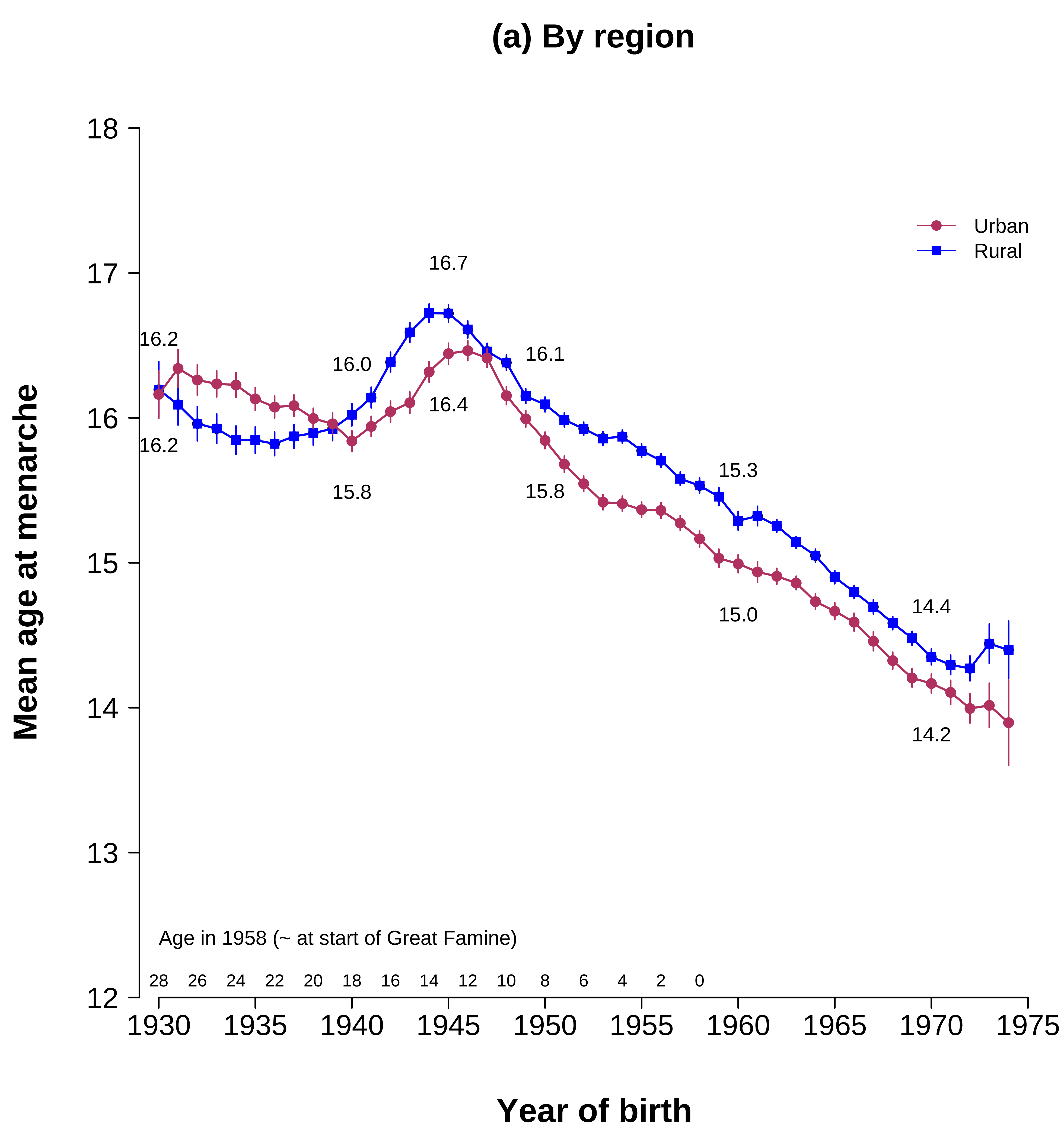
Values shown for 1930, 1940, 1945, 1950, 1960, 1970 and 1974 year−of−birth cohorts

Figure 2b. Mean age at menarche by year of birth within each area

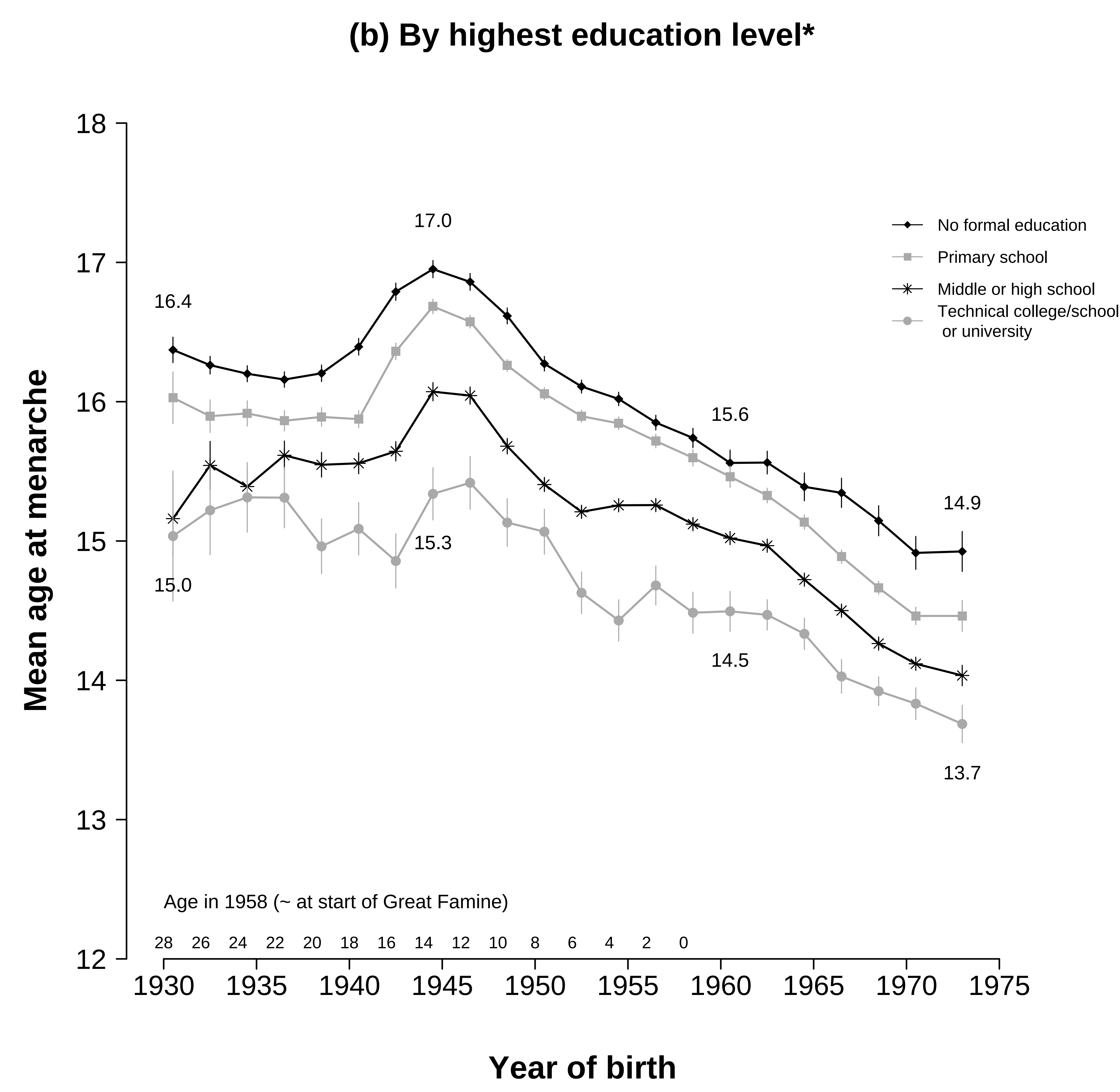


Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for earliest, 1945 and latest year−of−birth cohorts.

Figure 3. Area−adjusted mean age at menarche by year of birth in 302 180 women



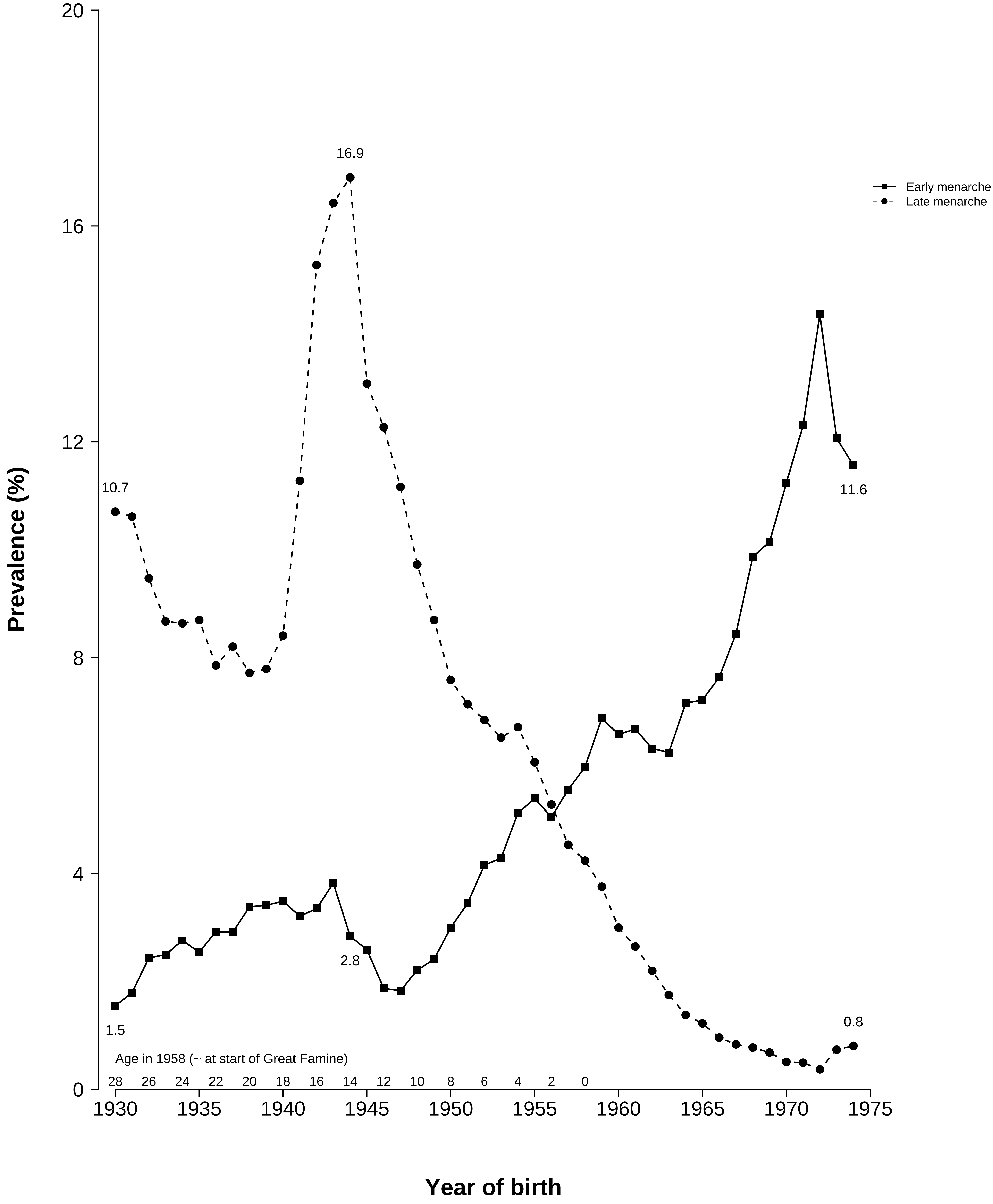
Values shown for 1930, 1940, 1945, 1950, 1960 and 1970 year−of−birth cohorts



*Combined means shown for each pair of year−of−birth groups starting 1930−1931 etc

Values shown for 1930−1, 1944−5, 1960−1 and 1973−4 year−of−birth cohorts

Figure 4. Area−adjusted prevalence of early and late menarche versus year of birth in 302 180 women

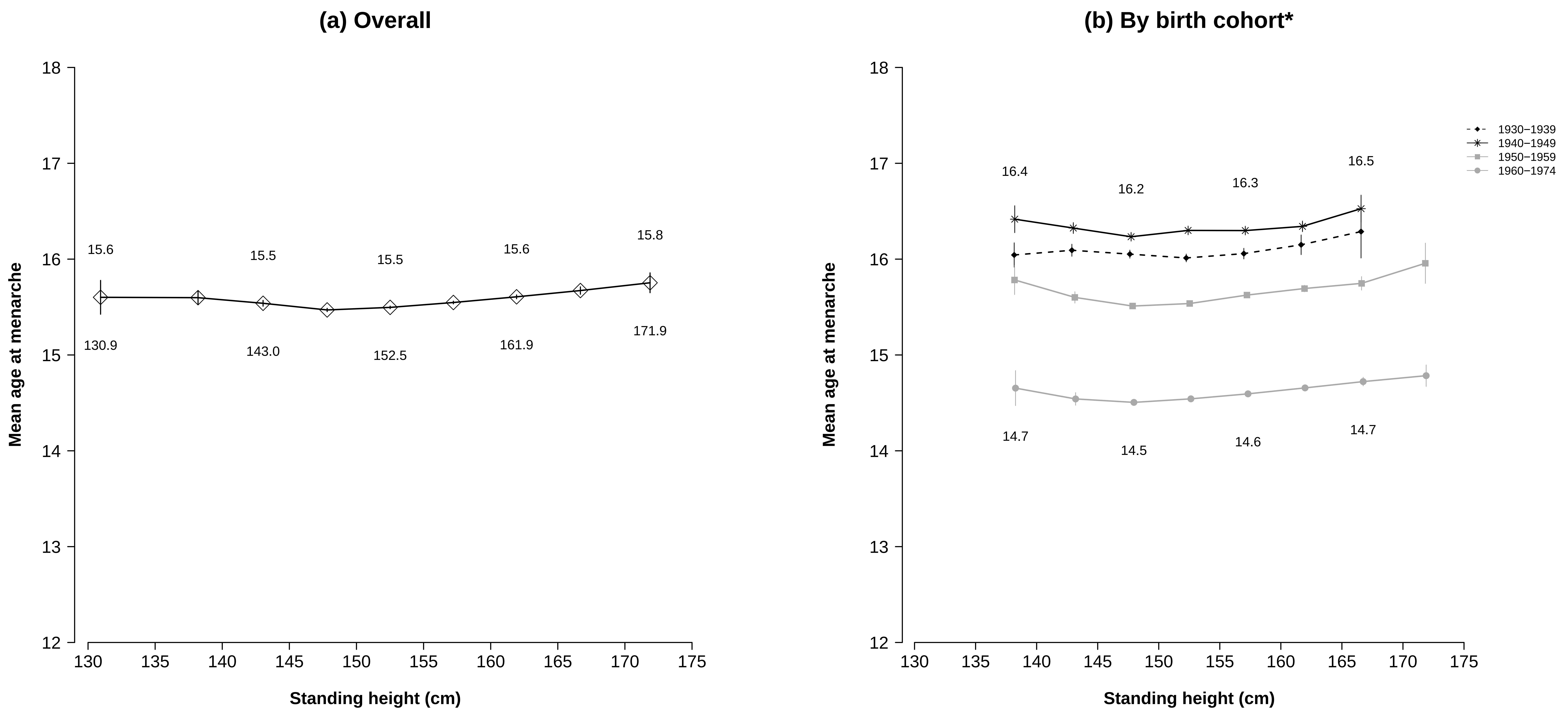


Early menarche: age at menarche <13

Late menarche: age at menarche >18

Values shown for 1930, 1944 and 1974 year−of−birth cohorts

Figure 5. Adjusted mean age at menarche versus adult standing height in 302 180 women

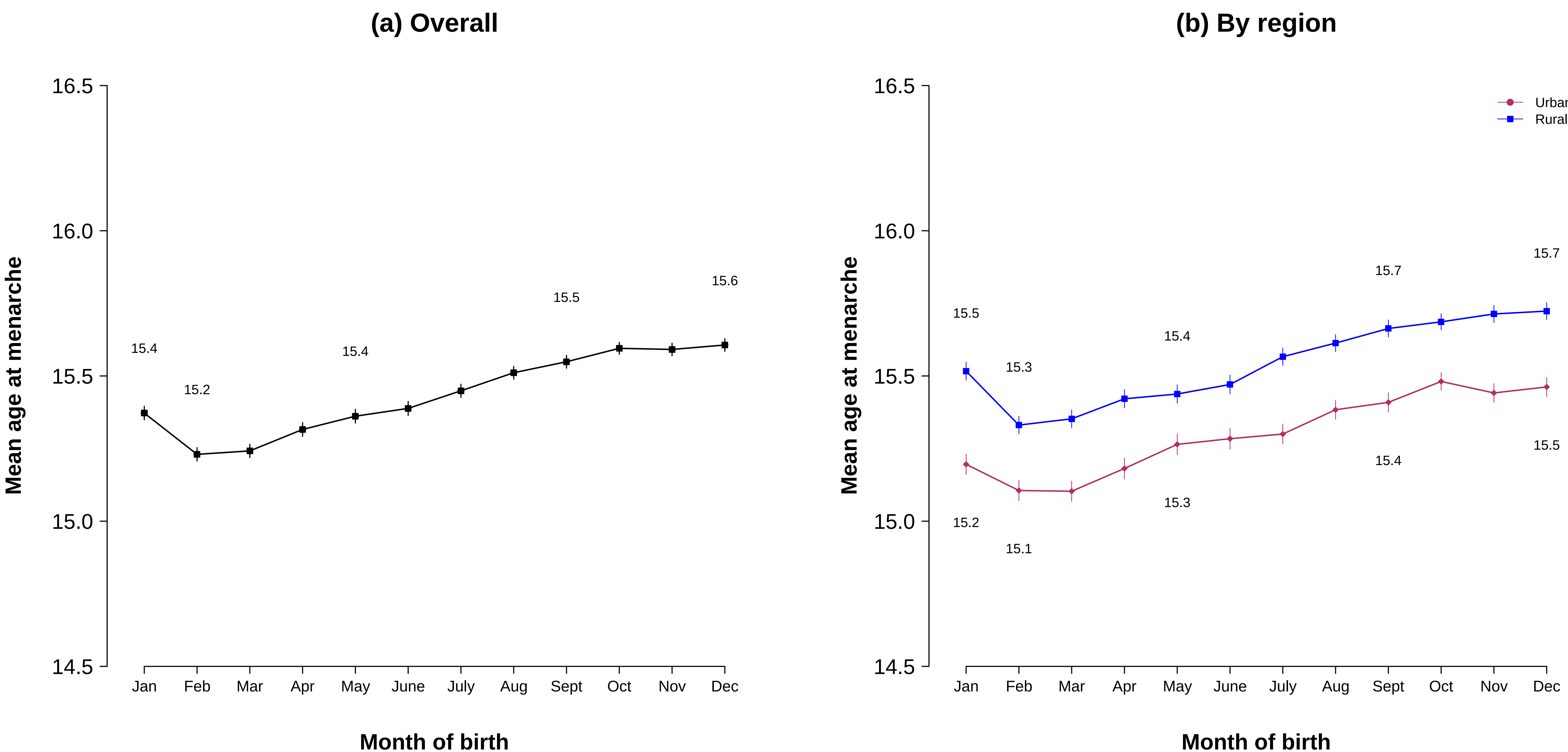


Means adjusted for region and year of birth

*Excludes any height range in which the number of women for a birth cohort in that range <150

Values shown for 1940−49 and 1960−74 birth cohorts

Figure 6. Area−adjusted mean age at menarche versus month of birth in 302 180 women



Values shown for January, February, May, September and December

Chapter 8.Age at menopause: regional variation, secular trend and main correlates

8.1 Results

8.1.1 Regional and socioeconomic variation in age at menopause

Overall, 89 320 naturally postmenopausal women from 10 areas aged ≥57 at baseline (born in 1930-51), with a similar number from urban and rural regions, were included in these analyses. Figure 1 shows the distribution of age at menopause in this subset of women overall and by urban and rural region, and Table 1 shows the mean age at menopause by area, region and year of birth. There was a normal distribution for age at menopause both overall and in urban and rural regions (Figure 1a-b), with a mean of 48.6 [SD 4.0] years and approximately 90% of women experiencing menopause in the age range 43-54 years (Figure 1a). Among urban and rural women, there was a clear digit preference for even numbers of years (Figure 1b). The adjusted mean age at menopause was 0.62 years higher in urban compared to rural women (48.95 versus 48.33 years, $p<0.0001$), but varied significantly between areas, especially rural areas (Table 1). Within urban areas, the mean adjusted age at menopause ranged from 48.60 years in Suzhou to 49.55 years in Qingdao ($\chi^2_{(4)} = 173$, $p<0.0001$) whereas within rural areas, it ranged from 47.76 years in Gansu to 48.94 years in Zhejiang ($\chi^2_{(4)} = 333$, $p<0.0001$: Table 1). Although the adjusted mean age at menopause was 0.55 years higher in coastal compared to inland areas ($p<0.0001$), no apparent difference was seen between northern and southern areas ($p=0.60$: Table 1).

Table 2 shows the association of age at menopause with education, occupation and annual household income, which was significant for all 3 factors although education again showed the strongest trend. Mean age at menopause increased with increasing level of education (Trend $\chi_{(1)}^2$ = 130, p<0.0001), so that women with tertiary-level education had menopause 0.95 years later than women with no formal schooling (p<0.0001). Annual household income showed a significant but weaker trend (Trend $\chi^2_{(1)}$ = 75, p<0.0001) so that women with the highest annual household income of ≥20 000 RMB also had menopause 0.39 years later than women with the lowest annual household income of <5000 RMB (48.82 versus 48.43 years, p<0.0001). There were also significant differences in mean age at menopause between women with different occupations ($\chi^2_{(3)}$ = 15, p=0.002), with women in manual occupations experiencing menopause earlier than those in non-manual occupations (48.56 versus 48.89 years: Table 2). No significant changes to the results were seen when each socioeconomic factor was adjusted for the others.

8.1.2 Secular trend in mean age at menopause

Figure 2 shows the secular trend of mean age at menopause across the 21 year-of birth cohorts included in the study overall (Figure 2a) and by region (Figure 2b). Among all women, the mean age at menopause increased by 1.4 years over 21 years from 47.8 years for women born in 1930 to 49.2 years for women born in 1951. The upward trend was approximately linear, increasing by 0.91 [SE 0.00] years for every 10 year-of-birth cohorts, with no deviation even for those who were exposed to famine at any age (Figure 2a and Table 1). A similar increasing trend was seen in urban and rural regions, but, across all year-of-birth cohorts, urban women had menopause later than rural women (Figure 2b).

8.1.3 Reproductive factors and age at menopause

The association of age at menopause with age at menarche is shown in Figure 3a and with age at first birth in Figure 3b. Overall, there was a U-shaped relationship between age at menarche and menopause, with the mean age at menopause increasing by approximately 0.22 [0.16] years per year later menarche for women with early menarche (i.e. <13 years) and 0.06 [0.01] years per year later menarche for women with menarche at ages 13-18. For women with late menarche (i.e. >18 years), the mean age at menopause decreased by 0.25 [0.04] years per year later menarche. Overall, there was a weak positive association of age at menopause with age at first live birth (Figure 3b), with the mean age at menopause increasing by approximately 0.03 [0.01] years per year later age at first live birth, although the association appeared to somewhat stronger for those with younger ages at first live birth.

Table 3 shows the relationship of mean age at menopause with gravidity, parity and OC use. Overall, a history of pregnancy was associated with a 2.10 (1.81-2.40) years delay in menopause ($p<0.0001$), that increased with increasing number of pregnancies. Compared to a mean age at menopause of 46.57 years among women who had never been pregnant, the mean age at menopause was 48.28, 48.70, and 48.76 years for those with 1-2, 3-5 and >5 pregnancies respectively (Trend $\chi_{(1)}^2 = 138$, $p<0.0001$). Similarly, among 88 432 women who had ever been pregnant, women with more than 5 births had menopause 1.37 years than nulliparous women, but the observed relationship was weaker than that seen for number of pregnancies (Trend $\chi_{(1)}^2 = 7$, $p=0.006$). No significant difference in mean age at menopause was observed between women with no still births and those with at least one such event (p=0.75). In this population of postmenopausal women, there was no reported current use of OCs at the baseline. However, the mean age at menopause was on average 0.33 (0.22-0.45) years later among women who reported previous OC use compared to those who had never used OCs (p<0.0001). Although age at menopause was not significantly associated with age at starting OC use (p=0.08), there was a weak increasing trend in age at menopause with duration of OC use (Trend $\chi_{(1)}^2 = 5$, p=0.02). Adjustment for level of education and annual household income did not significantly alter any of the above results for OC use.

Table 4 shows the association of age at menopause with breastfeeding and history of abortion overall and separately by urban and rural residence because of the large differences in the distribution of both reproductive factors between these regions (see Baseline Description: Results). Since both breastfeeding and abortions are strongly correlated with parity, means were further adjusted for number of live births or for number of pregnancies. Among all women, those who had ever breastfed had menopause 0.51 (0.25-0.76) years later than women who had never breastfed (p=0.0001), but the difference was smaller in urban women (0.29 years, p=0.04) and larger in rural women (0.73 years, p=0.001). Although there was a weak positive trend with duration of breastfeeding among rural women (Trend $\chi_{(1)}^2 = 5$, p=0.03), no significant association was seen either overall or among urban women (p=0.06 and 0.33 respectively). There was no significant association between age at menopause and history of spontaneous abortion either overall or by region (p=0.42 and 0.47 respectively). By contrast, women who reported at least one induced abortion had menopause 0.30 (0.18-0.42) years later than those who reported none, but again the difference was larger in rural women (0.39 years, p<0.0001) and smaller in urban women (0.22 years, p=0.0007). When the association with induced abortions was further adjusted for education to check for the effect of SES, the difference was attenuated both overall (0.24 years, $p<0.0001$) and in both urban (0.12 years, $p=0.05$) and rural women separately (0.35 years, $p<0.0001$).

8.1.4 Behavioural factors, BMI at age 25 and age at menopause

Table 5 shows the association of age at menopause with soy consumption, smoking and alcohol use. Apart from area and year of birth, means for all 3 factors were also adjusted for education to check for the effect of SES and means for alcohol history variables were further adjusted for smoking category given the overlap in drinking and smoking behaviour among CKB women (see Baseline Description: Results). Age at menopause was significantly associated with all 3 behavioural factors, with smoking showing the strongest trend. Mean age at menopause increased with increasing average consumption of soybean products (Trend $\chi_{(1)}^2$ = 13, $p=0.0004$), with women consuming soy products daily having menopause 0.33 (0.16–0.51) years later than women who never/rarely consumed soy products ($p=0.0002$). A history of smoking was shown to be associated with earlier onset of menopause, with women who had ever smoked experiencing menopause 0.34 (0.22-0.45) years earlier than women who had never smoked ($p<0.0001$). There was little difference in mean age at menopause between ex-regular and never smokers (48.64 versus 48.67 years) and – excluding ex-regular smokers – mean age at menopause decreased with increasing smoking frequency so that current regular smokers had menopause 0.54 years earlier than never smokers (Trend $\chi_{(1)}^2$ = 56, $p<0.0001$). Women who reported ever having consumed alcohol had menopause 0.16 (0.08-0.24) years later than women who reported no previous alcohol use ($p<0.0001$). However, there appeared to be a weak negative trend among women who currently drank (Trend $\chi_{(1)}^2$ = 6, $p=0.02$): mean age at menopause decreased with increasing frequency of alcohol use so that occasional drinkers had the highest mean age at menopause (48.79 years) with current regular drinkers experiencing menopause 0.26 years earlier (p=0.01).

Table 6 shows the association of age at menopause with BMI at age 25 which was calculated from current height and reported weight at age 25 among 65 762 women. There did not appear to be a significant association between age at menopause and BMI at age 25 either overall (p=0.83) or in either rural or urban women when regions were examined separately (data not shown).

8.2 Discussion

In this subset of 89 320 postmenopausal women aged ≥57 at baseline, the overall mean age at menopause was 48.6 years, with urban women experiencing menopause more than half a year later on average than rural women. Overall, mean age at menopause increased by 1.4 years over the 21 year-of-birth cohorts, with a similar secular trend in all areas, and no deviation was seen even for those women exposed to famine in their lifetime. Better SES was associated with a later age at menopause – with education showing the strongest trend – such that women with the highest level of education, the highest annual household income or non-manual occupations experienced menopause significantly later than women who were less educated, less wealthy or in manual occupations.

Age at menopause was significantly associated with several reproductive factors including gravidity, parity, OC use and breastfeeding, with a history of pregnancy having the biggest effect on age at menopause: women with at least one pregnancy experienced menopause 2 years later than women who had never been pregnant. Although soy consumption, smoking and alcohol use were all significantly associated with age at menopause, smoking showed the greatest effect, so that women who currently smoked had menopause 6 months earlier than women who had never smoked. Among CKB women, only number of pregnancies, number of live births, history of breastfeeding, smoking category and education were associated with more than 6 months difference in mean age at menopause between women in the highest and lowest categories of exposure.

8.2.1 Secular trend and regional and socioeconomic variation in age at menopause

CKB women experienced menopause in the same age range of 40-60 years as that seen currently in Western populations, although the mean was approximately 2.5 years lower [118], with women from the wealthier urban areas having menopause later. The digit preference seen in both urban and rural women reflects the uncertainty around the exact timing of menopause as it is usually diagnosed retrospectively following 12 months of amenorrhoea, unlike menarche which is a single discrete event. Despite this uncertainty, CKB women have shown good reproducibility of age at menopause (see Data Quality: Results).

Although mean age at menopause stagnated in a few populations, it has shown an increasing trend in most populations over the last century (see Literature Review: Age at menopause). Among CKB women, age at menopause showed a steadily increasing trend with a rate of increase that was comparable to the highest rates seen in American and European populations [48, 131, 134-137]. Notably, no deviation from the approximately linear secular trend was seen in this study, indicating that famine exposure at any time from *in utero* to adulthood did not have an effect on age at menopause at the population level. Despite a higher initial mean age at menopause in urban women, the rate of increase in the secular trend was similar for urban and rural women, suggesting that the main determinants of the increasing secular trend in age at menopause were the same in both regions.

Although most previous studies have found no association between age at menopause and socioeconomic factors, those few studies with significant results found that women with higher SES had later menopause (see Literature Review: Age at menopause). In this study, higher SES, as with urban residence, was also associated with later age at menopause; however, the 1.0, 0.3 and 0.4 year delays seen with tertiary education, non-manual occupations and high incomes respectively were smaller than those seen in the Shanghai Women's Study but comparable to several smaller studies on the effect of education [131, 133, 137, 146] and profession [42, 146] in other populations. Although this study's results were not significantly changed with adjustment for the other socioeconomic factors, as with age at menarche these associations most likely indicate the effect of other relevant exposures linked to SES on age at menopause. Urban women are more highly educated, more often employed in non-manual occupations and higher-earning, so differences in the pattern of exposures between urban and rural women approximate differences across SES groups. Given that patterns of alcohol use, smoking and soy consumption are similar for urban and rural women, it is more likely that reproductive factors such as parity which show large variation (see Results: Baseline Description) have an effect on age at menopause via SES. It is also highly likely that the significant differences seen with SES are partly due to residual confounding.

8.2.2 Reproductive factors and age at menopause

Previous studies in American and European populations have provided good evidence that an increasing number of pregnancies and live births are associated with a later age at menopause, but evidence on an association with other reproductive factors that affect oocyte numbers is equivocal. However, results from the Shanghai Women's Study of 33

054 postmenopausal urban Chinese women suggest that these factors may have an effect on age at menopause in this population, possibly due to different reproductive patterns and trends in China (see Literature Review: Age at menopause). Similarly, CKB women are unusual in that their fertility has been artificially altered by the introduction of compulsory family planning in China since the 1970s, which has produced a wider range of exposures in a relatively short time for both gravidity and parity compared to most other populations.

Overall, the findings in this study are consistent with the hypothesis that conservation of oocyte numbers may delay menopause: pregnancy, OC use and breastfeeding were associated with a later age at menopause. The strength of these associations was either comparable to or greater than that seen in other populations. For example, the significant delay of 1-2 years in menopause seen with increasing number of pregnancies and live births in this study is consistent with and similar in magnitude to that seen in other studies on this association [40, 42, 46, 131-133, 135-137, 139-143, 145, 146]. Similarly, the positive association of age at menopause with a history of breastfeeding is largely consistent with findings from the Shanghai Women's Study [143], although the effect of breastfeeding appears to be greater among rural women in CKB, probably due to rural women breastfeeding more often and for longer (see Baseline Description: Results). By comparison, the small but significant delay in menopause among women with at least one induced abortion contrasts with the absence of an effect reported by the Shanghai Women's Study [143]. This contrast may be partly due to the much smaller population in the latter study (which was also relatively homogenous in terms of reproductive patterns as it was confined to a single urban area) and to adjustment for more measures of SES, physical activity and energy intake. In China, induced abortion clinics are widely available and in some cases are provided free of charge by family planning services, but there may still be inequitable access to this service. In this study, the difference was attenuated with adjustment for education and it is possible that further attenuation would have been seen had better measures of SES been available, suggesting that residual confounding by factors that differ by SES – rather than the effect of an induced abortion itself – may account for this observed difference.

Although only a small proportion of women reported having ever used OCs in this study (two-thirds for only up to 3 years), there was a significant delay of 0.33 years among women who had past use of OCs compared to those with no use and a weak increase in age at menopause with increasing duration of OC use. These associations were robust to adjustment for SES, indicating that there was no selection bias for these analyses due to greater financial access to OCs as might be seen among urban women. These findings are generally compatible with those reported in a number of studies in Western populations (3756 Dutch women [48] and 2623 Polish women [133]) as well as the Shanghai Women's Study [143], where the estimated delay in menopause associated with a history of OC use ranged from 0.1-0.7 years. This range in the associated delay between studies may reflect differences in various other aspects of OC use (e.g. duration and type of OC used). Given the relatively poor reproducibility of OC use among CKB women (see Data Quality: Results), which would tend to attenuate an association towards the null [108], it is likely that the real association between age at menopause and OC use may in fact be somewhat stronger than observed.

8.2.3 Behavioural factors, BMI at age 25 and age at menopause

Unlike, reproductive factors, there is no single mechanism by which age at menopause may be linked to behavioural or anthropometric factors. It is most likely that these non-reproductive factors affect age at menopause through a range of mechanisms including direct action on the ovaries or modification of dropping sex hormone levels (see Literature Review: Age at menopause).

In Western populations, smoking around the time of menopause has been consistently associated with an earlier age at menopause, whereas it appears that former smokers have a similar age at menopause to non-smokers (see Literature Review: Age at menopause). Although only 5% of all women in CKB had ever smoked, they experienced menopause approximately 4 months earlier - current smokers 6 months earlier - than those who had never smoked, which was comparable to the lower end of the 0.4-2.0 years difference reported in most other populations [40, 45, 46, 48, 132-135, 137, 141-144, 146, 147, 155-158]. By comparison, existing evidence on the association of age at menopause with either alcohol or soy consumption is equivocal (see Literature Review: Age at menopause). The positive association between soy consumption and age at menopause in this study contrasts with the limited evidence from the Shanghai Women's Study [143] and a prospective cohort study of 1009 German women [45] that both failed to find an association. This inconsistency is possibly due to the greater geographical diversity and therefore a greater variety of diets in CKB, allowing detection of an effect across finer categories of increasing consumption. Similarly, although only 36% of CKB women had ever consumed alcohol, the absolute number of women was large enough to detect even a small effect on age at menopause independent of its association with smoking, which may not have been possible in other smaller studies in European, American and Chinese populations that found no association [45, 131, 133, 134, 143-145]. The associations between age at menopause and all 3 behavioural factors remained significant even after adjustment for education, indicating that the effect seen was not likely to be due to confounders mimicking the differences in patterns of smoking, alcohol use and soy consumption across SES groups.

Based on the few studies that have examined the association, there is no good evidence to suggest an effect of premenopausal BMI on age at menopause (see Literature Review: Age at menopause). The lack of an association between BMI at age 25 and age at menopause in this study – even when urban women were examined separately – differs from the Shanghai Women's Study that reported a weak trend with BMI at age 20 suggesting increasing BMI during early adulthood (at age 20) may predict a later age at menopause. Although CKB used self-reported BMI at age 25, there was good reproducibility of this variable (see Results: Data Quality) among a large number of women, which makes it unlikely that a real association was missed due to either insufficient numbers of women or random measurement error. It is not clear why this study should contrast with the Shanghai Women's Study, but residual confounding may be responsible as the latter study adjusted the association for more indicators of SES and other reproductive factors whereas this study only adjusted for area and year of birth.

8.3 Conclusion

Among a subset of 89 320 women aged ≥57, age at menopause has steadily increased by 1.4 years over 21 year-of-birth cohorts and, unlike age at menarche, no major disruption of the secular trend coinciding with the Great Chinese Famine was apparent. Age at menopause was significantly associated with several reproductive, socioeconomic and behavioural factors (with current smokers having menopause much earlier than their non-smoking counterparts), but gravidity had by far the biggest effect. The significant associations with socioeconomic factors – as with age at menarche – most likely reflect the effect of other exposures that differ by SES e.g. reproductive patterns as well as residual confounding. The positive findings in this study contrast in many instances with often equivocal findings of other studies, including the Shanghai Women's Study – notably the only other large study of the correlates of age at menopause in a Chinese population. This is probably due to the inclusion of a much larger, more heterogeneous population with different patterns and range of exposures in CKB which permits reliable detection of small effects across finer categories of exposure.

This study therefore adds new information to the current evidence on the secular trend in age at menopause as well as reproductive, behavioural and socioeconomic correlates of age at menopause in a large heterogeneous Chinese population. Although CKB women have different patterns of exposure to most other populations studied so far, these findings may also be relevant more generally, particularly for correlates where there is very limited evidence to date.

Table 1. Mean age at menopause by 5 year birth cohort and region

Region	No of women	Year of birth 1930-34	1935-39	1940-44	1945-51	All year-of-birth groups	(95% CI)[1]	Test statistic
Urban (Name of city)								
Harbin	12029	48.56	48.59	48.92	49.58	49.04	(48.96-49.12)	
Qingdao	5789	48.56	49.04	49.71	50.06	49.55	(49.43-49.66)	
Suzhou	9520	47.20	47.71	49.00	49.29	48.60	(48.51-48.69)	
Liuzhou	10810	48.32	48.52	48.70	49.32	48.85	(48.77-48.94)	
Haikou	6521	48.06	48.39	48.98	49.62	48.96	(48.85-49.07)	$\chi^2_{(4)}$= 173 (p<0.0001)[2]
Rural (Name of province)								
Zhejiang	10551	47.83	48.54	49.09	49.43	48.94	(48.86-49.03)	
Hunan	9268	47.19	47.92	48.51	48.83	48.35	(48.26-48.44)	
Henan	8877	47.34	47.90	48.39	48.67	48.25	(48.16-48.34)	
Sichuan	9404	47.38	47.70	48.26	48.48	48.10	(48.01-48.19)	$\chi^2_{(4)}$= 333 (p<0.0001)[2]
Gansu	6551	47.43	47.45	47.85	48.07	47.76	(47.66-47.87)	$\chi^2_{(9)}$= 946 (p<0.0001)[2]
Region								
Urban	44669	48.13	48.45	48.99	49.52	48.95	(48.91-49.00)	
Rural	44651	47.46	47.95	48.46	48.76	48.33	(48.29-48.37)	
Difference						**0.62**	**(0.56-0.68)**	z=21 (p<0.0001)
Northernmost 5	42766	47.85	48.23	48.75	49.09	48.65	(48.61-48.69)	
Southernmost 5	46554	47.83	48.23	48.69	49.12	48.64	(48.60-48.68)	
Difference						**0.02**	**(-0.04-0.07)**	z=1 (p=0.6)
Coastal 5	43191	47.95	48.41	49.03	49.48	48.93	(48.89-48.97)	
Inland 5	46129	47.72	48.05	48.45	48.74	48.38	(48.34-48.42)	
Difference						**0.55**	**(0.49-0.61)**	z=18 (p<0.0001)
All regions	**52459**	**47.80**	**48.18**	**48.74**	**49.13**	**48.64**	**(48.61-48.67)**	$\chi^2_{(Trend)}$= 993 (p<0.0001)

[1]Adjusted for year of birth

[2]Test for heterogeneity

Table 2. Mean age at menopause versus socioeconomic factors

Socioeconomic factor	No of women (n=89 320)	Mean age at menopause (95% CI)	Test statistic
Education level			
No formal school	36495	48.48 (48.43-48.53)	
Primary School	32959	48.65 (48.60-48.70)	
Middle or High School	17328	48.86 (48.79-48.93)	
Technical school or University	2538	49.43 (49.25-49.61)	$\chi^2_{(Trend)}$=130
Difference[2]		**0.95 (0.75- 1.14)**	(p<0.0001)
Current occupation			
Manual	28806	48.56 (48.50-48.63)	
Non-manual	1464	48.89 (48.66-49.13)	
Not currently working	57279	48.68 (48.64-48.72)	$\chi^2_{(3)}$= 15
Other	1771	48.52 (48.31-48.74)	(p=0.002)[3]
Annual household income (RMB)			
<5000	16128	48.43 (48.36-48.51)	
5000-19 999	41494	48.59 (48.55-48.64)	
≥20 000	31698	48.82 (48.77-48.87)	$\chi^2_{(Trend)}$=75
Difference[2]		**0.39 (0.29- 0.48)**	(p<0.0001)

[1]Adjusted for area and year of birth
[2]Difference between bottom and top category
[3]Test for heterogeneity

Table 3. Mean age at menopause versus selected reproductive factors in all women

Reproductive factor	No of women	Mean year-of-birth	Mean[1] age at menopause	(95% CI)	Test statistic
<u>Gravidity and parity</u>					
History of pregnancy (n= 89 320)					
No	888	1941	46.56	(46.27-46.85)	
Yes	88432	1942	48.66	(48.64-48.69)	
Difference			**2.10**	**(1.81- 2.40)**	**z=14 (p<0.0001)**
No of pregnancies (n= 89 320)					
0	888	1941	46.57	(46.28-46.86)	
1 to 2	9948	1944	48.28	(48.19-48.37)	
3 to 5	56984	1942	48.70	(48.66-48.73)	
>5	21500	1939	48.76	(48.69-48.82)	$\chi^2_{(Trend)}$=138
Difference[2]			**2.19**	**(1.89- 2.48)**	**(p<0.0001)**
No of live births (n= 88432)					
0	282	1940	47.36	(46.84-47.88)	
1 to 3	24730	1944	48.63	(48.57-48.69)	
3 to 5	55589	1941	48.68	(48.64-48.72)	
>5	7831	1937	48.73	(48.62-48.84)	$\chi^2_{(Trend)}$=7
Difference[2]			**1.37**	**(0.84- 1.90)**	**(p=0.006)**
No of still births (n= 88 432)					
0	78989	1942	48.66	(48.63-48.69)	
≥1	6672	1941	48.68	(48.58-48.78)	
Difference			**0.02**	**(-0.08- 0.11)**	**z=0 (p=0.75)**
<u>Oral contraceptive use</u>					
History of OC use[3] (n= 89 320)					
Never	81749	1942	48.62	(48.58-48.65)	
Past use	7571	1943	48.95	(48.85-49.05)	
Difference			**0.33**	**(0.22-0.45)**	**z=6 (p<0.0001)**
Age started OC use (n= 7571)[4]					
≤25	1895	1945	48.81	(48.61-49.02)	
26-30	3225	1943	48.95	(48.79-49.10)	
>30	2451	1941	49.06	(48.88-49.23)	$\chi^2_{(Trend)}$=3
Difference[2]			**0.21**	**(-0.06-0.49)**	**(p=0.08)**
Duration of OC use in years (n= 7571)[5]					
<2	3025	1943	48.83	(48.67-48.99)	
2-3	2006	1943	48.93	(48.73-49.13)	
≥4	2540	1943	49.11	(48.93-49.28)	$\chi^2_{(Trend)}$=5
Difference[2]			**0.24**	**(0.00-0.47)**	**(p=0.02)**

[1]Adjusted for area and year of birth
[2]Difference between bottom and top category
[3]No woman in this population reported current OC use
[4]Also adjusted for duration of OC use
[5]Also adjusted for age at starting OC use

Table 4. Mean age at menopause versus selected reproductive factors overall and by urban and rural residence

	Urban			Rural			Overall		
Reproductive factor	**No of women**	**Mean[1] age at menopause (95% CI)**	**Test statistic**	**No of women**	**Mean[1] age at menopause (95% CI)**	**Test statistic**	**No of women**	**Mean[1] age at menopause (95% CI)**	**Test statistic**
<u>Breastfeeding (n= 88 150)</u>									
History of breastfeeding									
No	1030	48.70 (48.43-48.97)		401	47.63 (47.20-48.07)		1431	48.40 (48.17-48.63)	
Yes	43071	48.98 (48.94-49.03)		43648	48.37 (48.33-48.41)		86719	48.67 (48.64-48.70)	
No. missing	568			602			1170		
Difference		**0.29 (0.01-0.56)**	**z=2 (p=0.04)**		**0.73 (0.30-1.16)**	**z=3 (p=0.001)**		**0.51 (0.25-0.76)**	**z=4 (p=0.0001)**
Average length of breastfeeding									
No breastfeeding	1030	48.66 (48.39-48.93)		401	47.63 (47.20-48.06)		1431	48.37 (48.14-48.60)	
≤ 6	2170	48.66 (48.48-48.85)		1134	48.25 (47.99-48.50)		3304	48.52 (48.37-48.67)	
7-12	24065	48.99 (48.94-49.05)		13766	48.55 (48.48-48.63)		37831	48.83 (48.79-48.88)	
13-18	9132	49.09 (48.99-49.18)		12133	48.43 (48.35-48.51)		21265	48.71 (48.65-48.77)	
19-24	5490	48.89 (48.78-49.01)	**$\chi^2_{(Trend)}=1$**	10710	48.22 (48.14-48.31)	**$\chi^2_{(Trend)}=5$**	16200	48.45 (48.38-48.52)	**$\chi^2_{(Trend)}=4$**
>24	2214	48.75 (48.56-48.93)	**(p=0.33)[3]**	5905	48.21 (48.10-48.32)	**(p=0.03)[3]**	8119	48.36 (48.26-48.45)	**(p=0.06)[3]**
<u>History of abortion (n=88 432)</u>									
No of spontaneous abortions									
0	39936	48.97 (48.93-49.01)		37605	48.33 (48.29-48.38)		77541	48.66 (48.63-48.69)	
≥1	4293	49.07 (48.94-49.21)		6598	48.44 (48.33-48.55)		10891	48.69 (48.61-48.77)	
Difference		**0.08 (-0.13-0.30)**	**z=1 (p=0.47)**		**0.08 (-0.14-0.29)**	**z=1 (p=0.47)**		**0.08 (-0.12- 0.28)**	**z=1 (p=0.42)**
No of induced abortions									
0	18013	48.85 (48.78-48.91)		31450	48.24 (48.19-48.29)		49463	48.46 (48.42-48.50)	
≥1	26216	49.07 (49.01-49.12)		12753	48.63 (48.55-48.71)		38969	48.92 (48.88-48.97)	
Difference		**0.22 (0.10-0.33)**	**z=3 (p=0.0007)**		**0.39 (0.25-0.52)**	**z=6 (p<0.0001)**		**0.30 (0.18- 0.42)**	**z=5 (p<0.0001)**

[1]Adjusted for area and year of birth (as well as number of live births for length of breastfeeding analyses and number of pregnancies for history of abortion analyses)

[2]Difference between bottom and top category (excludes women with no history of breastfeeding)

[3]Excludes women with no history of breastfeeding

Table 5. Mean age at menopause versus behavioural factors

Behavioural factor	No of women (n= 89 320)	Mean[1] age at menopause (95%CI)	Test statistic
Diet			
Average soy consumption over last year			
Never/rarely	10446	48.59 (48.50-48.69)	
Monthly	25273	48.59 (48.53-48.65)	
1-3 days per week	44355	48.66 (48.62-48.70)	
4-6 days per week	5445	48.64 (48.52-48.76)	
Daily	3801	48.93 (48.79-49.07)	$\chi^2_{(Trend)}$=13
Difference[2]		**0.33 (0.16- 0.51)**	**(p=0.0004)**
Smoking history			
Any history of smoking			
No	81128	48.67 (48.64-48.71)	
Yes	8192	48.34 (48.23-48.44)	
Difference		**0.34 (0.22-0.45)**	**z=6 (p<0.0001)**
Smoking category			
Never smoker	81128	48.67 (48.64-48.70)	
Occasional smoker	1999	48.46 (48.27-48.66)	
Current regular smoker	4162	48.14 (48.00-48.28)	
Ex regular smoker	2031	48.64 (48.44-48.84)	$\chi^2_{(Trend)}$=56
Difference[3]		**0.54 (0.40-0.67)**	**(p<0.0001)[4]**
Alcohol history			
Any history of alcohol use			
No	62934	48.60 (48.56-48.63)	
Yes	26386	48.76 (48.70-48.82)	
Difference		**0.16 (0.08- 0.24)**	**z=4 (p<0.0001)**
Alcohol use category			
Non-drinker	62934	48.59 (48.56-48.63)	
Occasional drinker	22146	48.79 (48.72-48.85)	
Monthly drinker	835	48.73 (48.43-49.03)	
Current regular drinker	2120	48.52 (48.33-48.72)	
Ex-regular drinker	1285	48.69 (48.45-48.94)	$\chi^2_{(Trend)}$=6
Difference[5]		**0.26 (0.07-0.46)**	**(p=0.02)[6]**

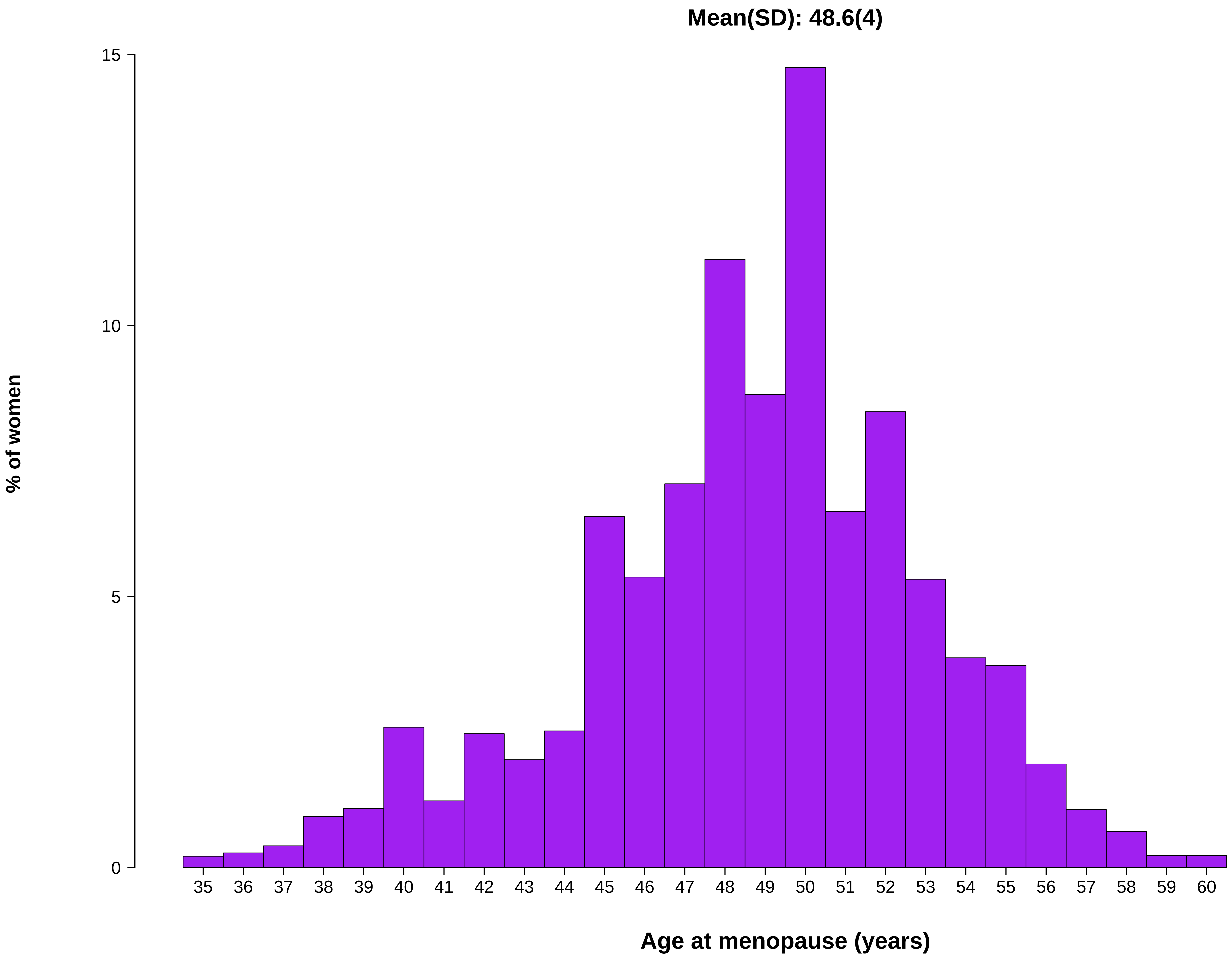
[1]Adjusted for area, year of birth and education (as well as smoking category for alcohol history analyses)
[2]Difference between daily and never/rarely categories
[3]Difference between never and current regular smokers
[4]Excludes ex-regular smokers
[5]Difference between occasional and current regular drinkers
[6]Excludes non-drinkers and ex-regular drinkers

Table 6. Mean age at menopause versus BMI at age 25

BMI at age 25 (kg/m²)	No of women (n= 65 762)	Mean[1] age at menopause (95% CI)	Test statistic
<20	8093	48.67 (48.58-48.77)	
20-21	14994	48.84 (48.77-48.91)	
22-23	17457	48.88 (48.81-48.94)	
24-25	13140	48.83 (48.76-48.91)	**$\chi^2_{(Trend)}$=0**
≥26	12078	48.76 (48.68-48.83)	**(p=0.63)**
Change in age at menopause per 1kg/m² increase in BMI at age 25 (years)		-0.001	**(p= 0.83)**

[1]Adjusted for area and year of birth

Figure 1a: Proportion of women by age at menopause



Note: Only women with age at menopause in range 35−60 years shown

Figure 1b. Proportion of women by age at menopause in urban and rural women

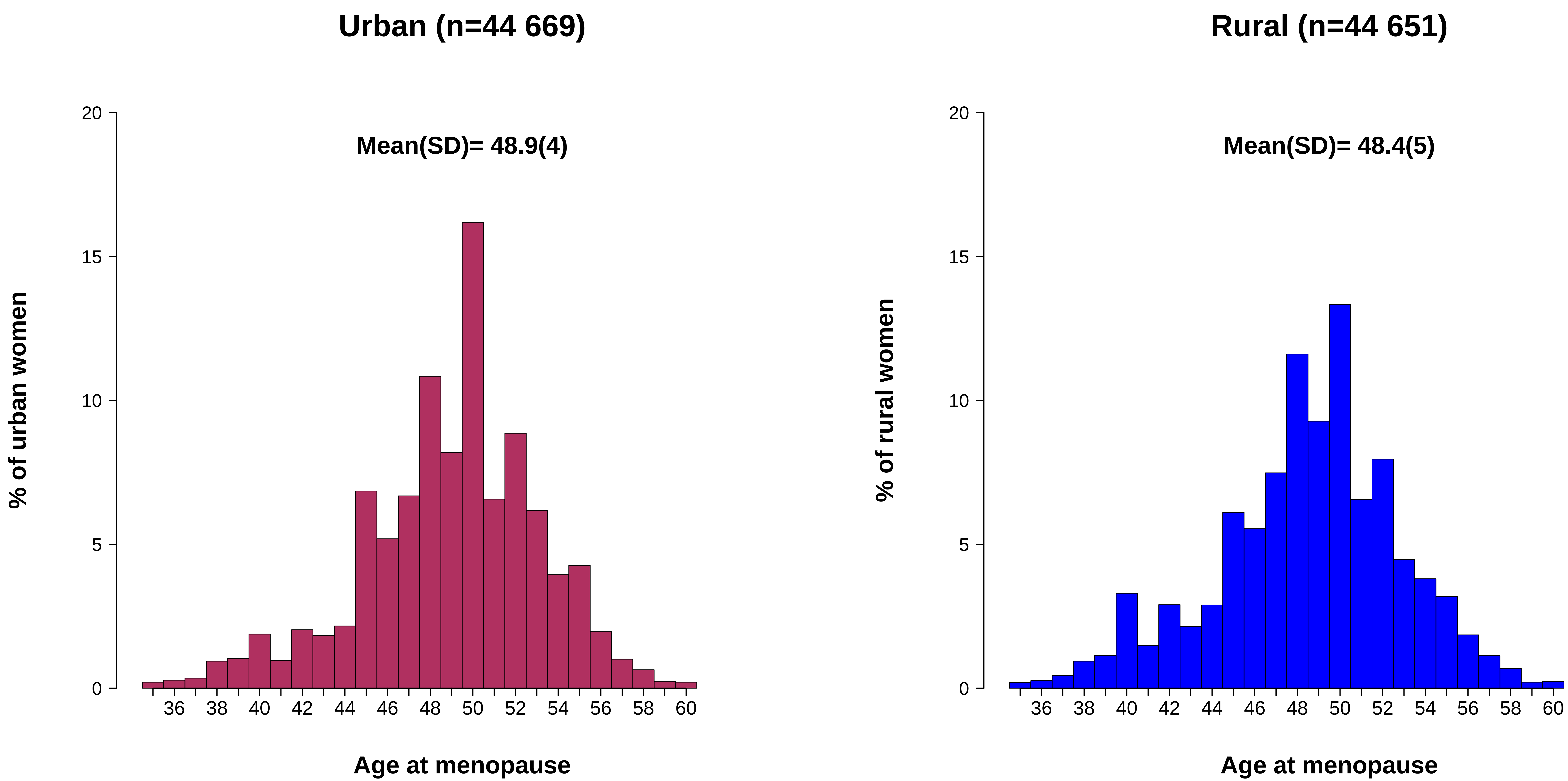
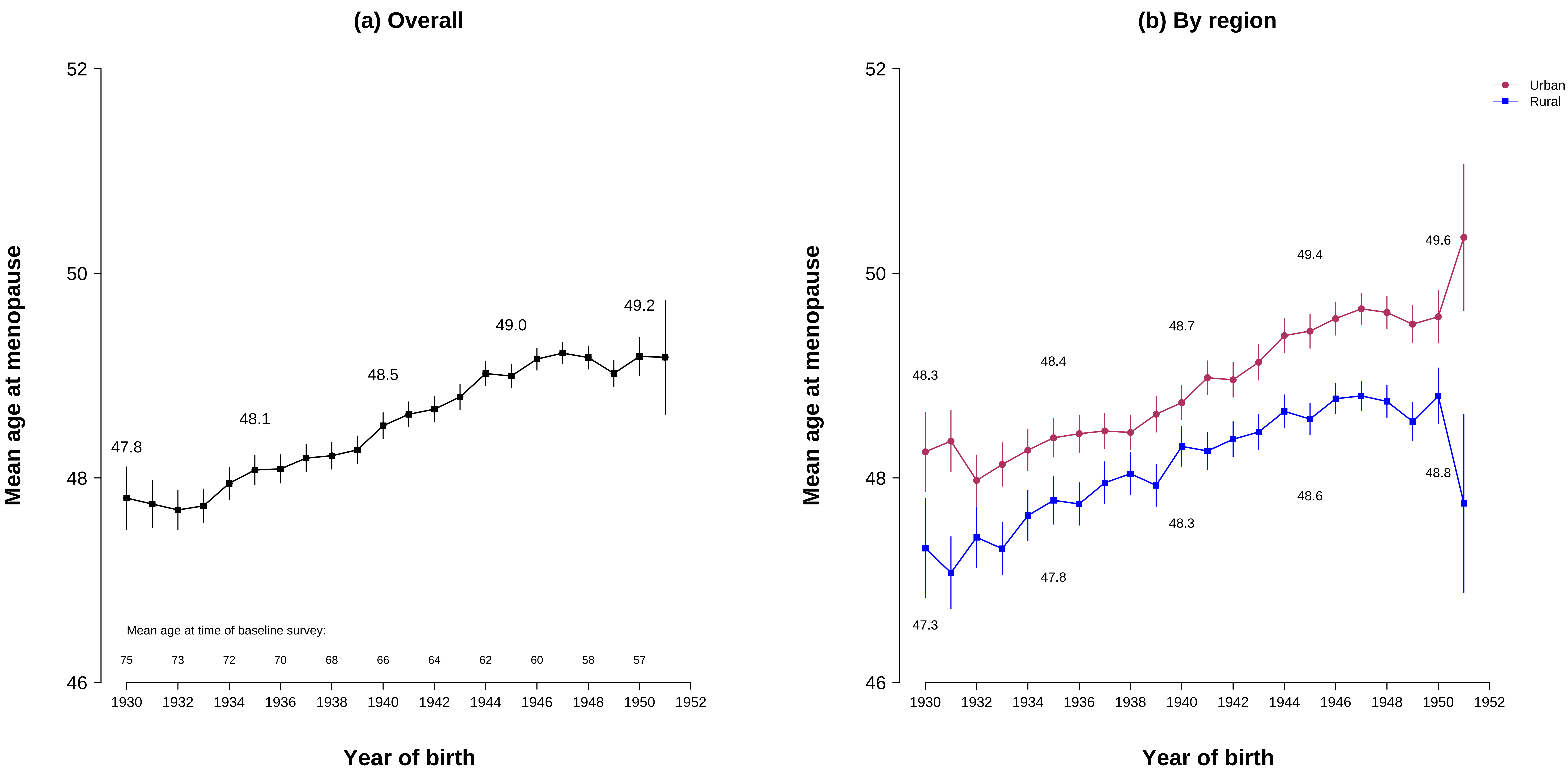
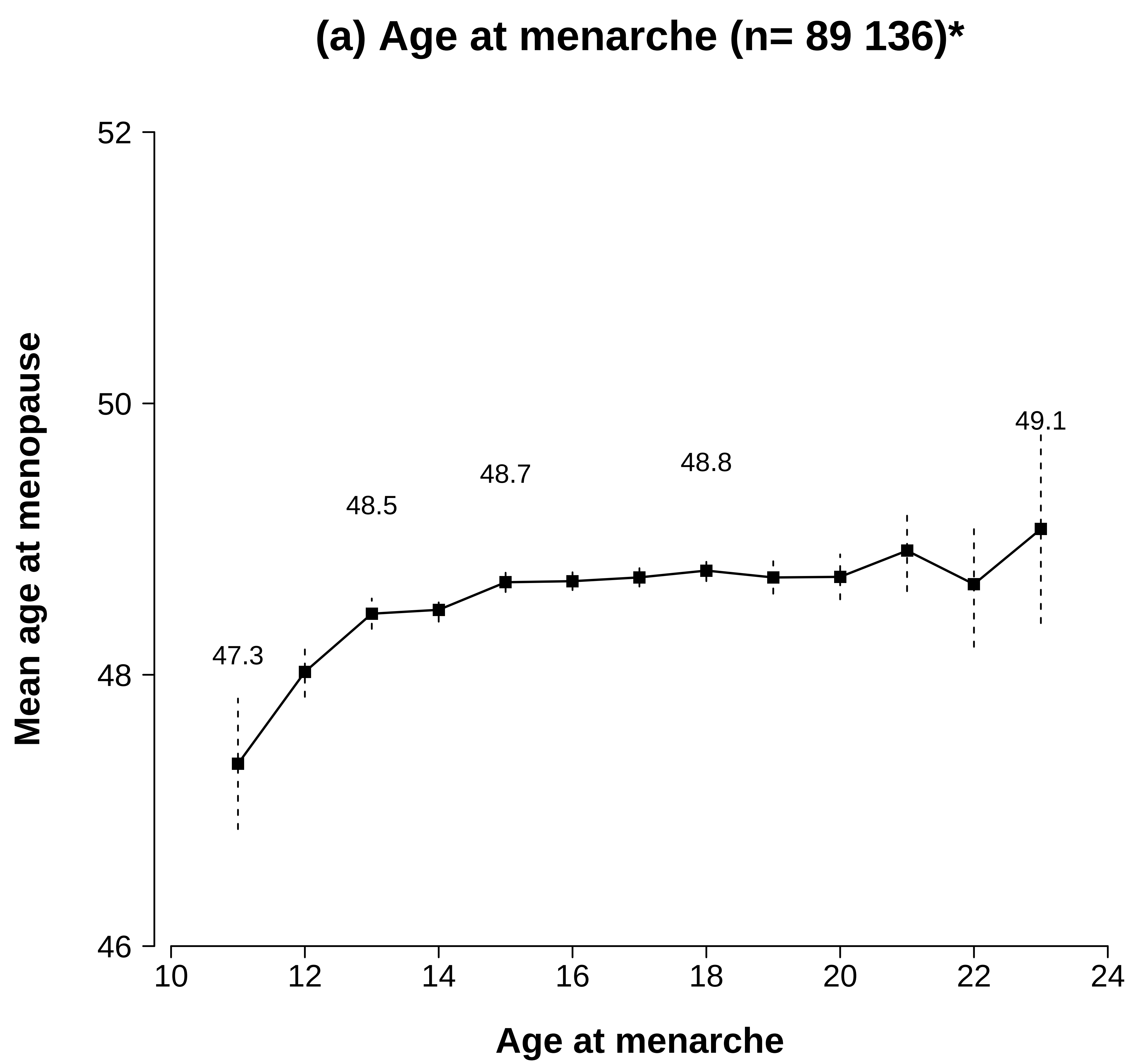


Figure 2: Area−adjusted mean age at menopause by year of birth in 89 320 women



Values shown for 1930, 1935, 1940, 1945 and 1950 year−of−birth cohorts

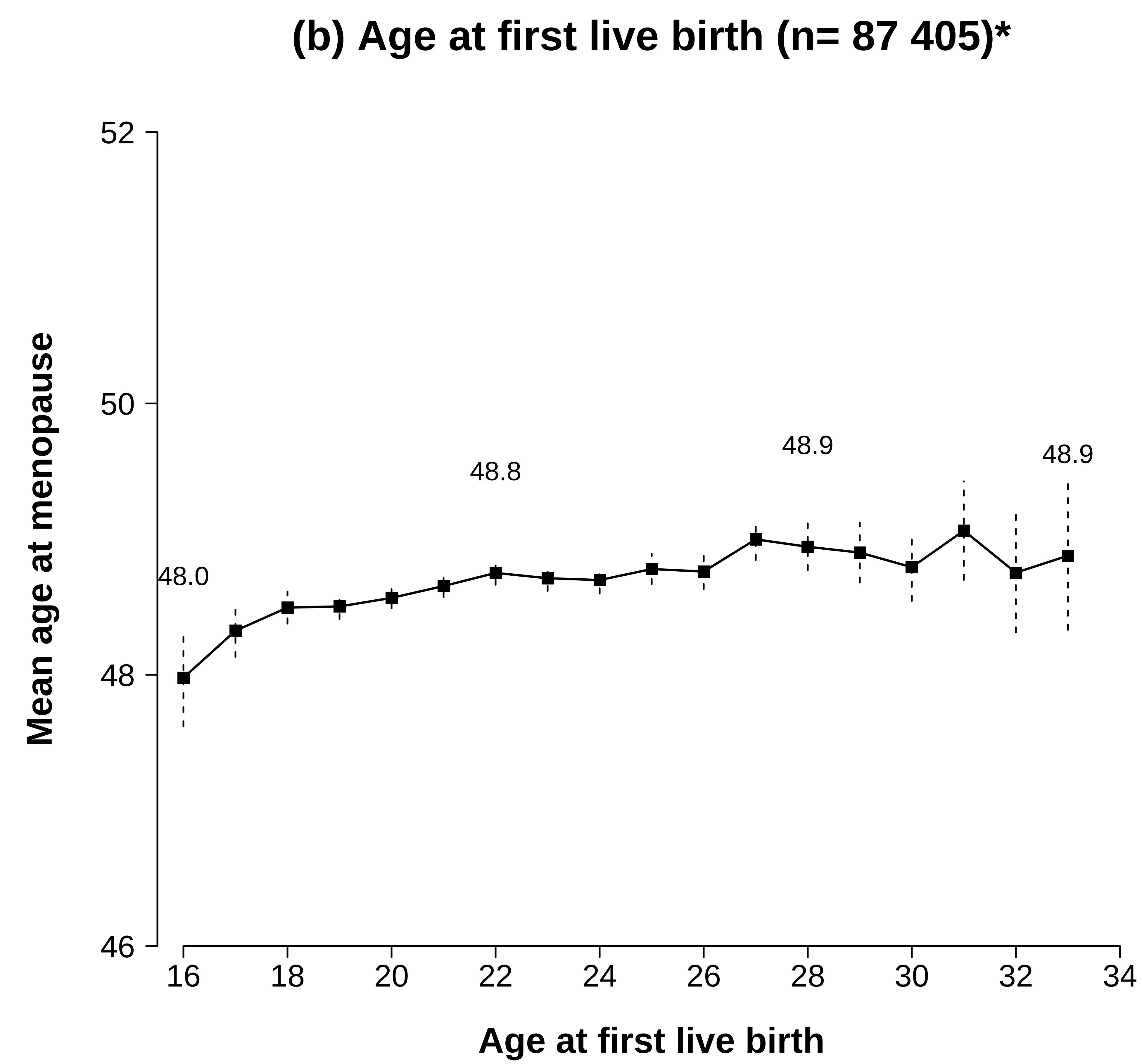
Figure 3: Adjusted mean age at menopause versus selected reproductive variables



Means adjusted for area and year of birth

*Excludes a total of 184 women from those ages at menarche with <100 women

Values shown where age at menarche= 11, 13, 15, 18 and 23



Means adjusted for area and year of birth

*Excludes a total of 745 women from those ages at first birth with <200 women

Values shown where age at first birth= 16, 22, 28 and 33

Chapter 9. Association of age at menarche and age at menopause with selected CVD risk factors

9.1 Results

9.1.1 Secular trends of physical characteristics

Figures 1 and 2 show the secular trends of selected physical characteristics among 302 180 women separately by urban and rural region across 44 year-of-birth cohorts, and Figures 3a-i show the same trends separately within each area. Table 1 gives the change in each physical characteristic per 10 year-of-birth cohorts. As expected, the secular trends mirrored to some extent the age-related trends seen for these same factors (see Baseline Description: Results), with similarly significant differences between urban and rural women in some cases (Table 1).

SBP is the only variable that showed a linear decrease of 8.6 [SE 0.05] mmHg per 10 year-of-birth cohorts (Figure 1a), with somewhat steeper changes in urban than rural women (8.8mmHg versus 8.4mmHg 10 year-of-birth cohorts, $p<0.0001$: Table 1) although urban women maintained a lower mean SBP for all year-of-birth cohorts (Figure 1a). Although there was a decreasing linear trend in every area, the apparent rate of decline varied from 7.1mmHg per 10 year-of-birth cohorts in Suzhou and Sichuan to 9.1mmHg per 10 year-of-birth cohorts in Qingdao (Figure 3a). By contrast, DBP showed an inverted U-shaped trend, with greater changes among urban women across all year-of-birth cohorts ($F=13$, $p=0.0004$ and $F=154$, $p<0.0001$: Figure 1b, Table 1). There was large variation between areas with Zhejiang, Suzhou, Sichuan and Gansu showing very little change in DBP across year-of-birth cohorts compared to regions such as Harbin, Qingdao and Haikou (Figure 3b).

Standing height was the only variable to show a linear increasing secular trend, with height increasing by 1.8 [0.01] cm per 10 year-of-birth cohorts overall (Figure 1, Table 1). Although rural women had a greater overall increase in height (7.2cm versus 6.9cm) and urban women were taller in all year-of-birth cohorts (Figure 1c), the total increase over 38 year-of-birth cohorts varied between areas from 6.4cm in Haikou to 8.5cm in Suzhou (Figure 3c).

BMI also showed an inverted U-shaped trend that differed between urban and rural women, with an apparent overall decrease for urban women that was approximately twice as large as the apparent increase for rural women over 40 year-of-birth cohorts (Figure 1d). There were greater changes in BMI among rural women across all year-of-birth cohorts, so that the trends became more closely aligned for urban and rural women born from 1960 onwards ($F=12$, $p=0.0004$ post-1960 versus 159 pre-1950, $p<0.0001$: Figure 1d, Table 1). There were distinct differences in BMI trends between areas, from a steadily decreasing trend in Qingdao to more flattened trends in Liuzhou and Henan to inverted U-shaped trends in Harbin, Hunan, Suzhou and Haikou (Figure 3d).

Weight, BFP, WC, HC and WHR all showed different patterns between urban and rural women (Table 1, Figures 2a-e), with greater changes in weight, BFP and HC for earlier year-of-birth cohorts ($p<0.0001$), and greater changes in weight for later year-of-birth cohorts ($p=0.007$: Table 1) among rural women. There was no apparent change in WHR with later year of birth among urban women born in 1930-40 and among rural women born in 1930-50 before both trends appeared to decline (Table 1, Figure 2e). This trend in WHR reflected the different trends for WC and HC where rural women appeared to have a greater and longer period of increase in HC and urban women a much greater and earlier rate of decline in WC (Table 1, Figure 2c-e). Despite large variation in trends for all anthropometric variables between both urban and rural areas, women in Qingdao showed the greatest overall change (Figures 3e-i).

9.1.2 Association of blood pressure and anthropometry with age at menarche

Table 2 shows the change in blood pressure and anthropometry per 10 years later menarche and Figures 4-5 show anthropometric and blood pressure variables plotted against the ages at menarche with >1000 women (i.e. 11 to 21 years) among 302 180 women born in 1930-74. All anthropometric variables showed significant inverse associations with age at menarche in both urban and rural women (Figures 4a-f). Current BMI, BMI at age 25, BFP, WC, HC and WHR all decreased linearly with increasing age at menarche by 2.0 [0.03] kg/m^2, 0.7 [0.03] kg/m^2, 3.4 [0.07] %, 3.8 [0.09] cm, 2.8 [0.06] cm and 0.02 [0.001] per 10 years later menarche respectively ($p<0.0001$ for all: Table 2). Notably, current BMI was twice as strongly associated with age at menarche compared to BMI at age 25 (2.0kg/m^2 versus 0.7kg/m^2 per 10 years later menarche: Table 2). The strength of the associations with anthropometry was greater – in some cases up to twice as strong – in rural compared to urban women ($p<0.0001$ for all: Table 2). WC was more strongly associated with age at menarche than HC in rural women (3.8 cm versus 2.8 cm per 10 years later menarche, $p<0.0001$: Table 2) but the associations showed similar strengths in urban women (3.0 cm versus 2.9 cm per 10 years later menarche, p<0.0001: Table 2). As a result, WHR was twice as strongly associated with age at menarche in rural compared to urban women (0.02 versus 0.01 per 10 years later menarche, p<0.0001: Table 2).

The significant inverse associations of SBP and DBP with age at menarche were mostly attenuated following adjustment for current BMI to no or marginal significance in urban women although they remained statistically significant in rural women. Overall, mean SBP adjusted for area and year of birth decreased linearly by 4.8 [0.20] mmHg per 10 years later menarche (p<0.0001: Table 2, Figure 5a), which was attenuated by over half to 2.0 [0.19] mmHg when adjusted for current BMI (p<0.0001: Table 2, Figure 5b). The association with SBP was almost twice as strong in rural compared to urban women (6.2mmHg versus 3.2mmHg per 10 years later menarche, p<0.0001), but both associations were attenuated by at least half with adjustment for BMI to 0.5mmHg and 3.1mmHg per 10 years later menarche in urban and rural women respectively (p=0.05 and p<0.0001: Table 2). Similarly, mean DBP adjusted for area and year of birth decreased linearly by 2.3 [0.11] mmHg per 10 years later menarche (p<0.0001: Table 2, Figure 5c) and was also attenuated by over half to 0.9 [0.10] mmHg when adjusted for BMI (p<0.0001: Figure 5d). Again, the strength of the association with DBP in rural women was almost twice that in urban women (2.9 mmHg versus 1.6 mmHg per 10 years later menarche, both p<0.0001: Table 2), but was attenuated by over half with adjustment for BMI to 0.3mmHg and 1.3mmHg per 10 years later menarche in urban and rural women respectively (p=0.07 and p<0.0001: Table 2).

9.1.3 Association of blood pressure and anthropometry with age at menopause

Table 3 shows the change in blood pressure and anthropometry per 10 years later menopause and Figures 6-7 show anthropometric and blood pressure variables plotted against ages at menopause with > 1000 women (i.e. 40 and 56 years) among 89 320 naturally postmenopausal women born in 1930-51. In contrast to age at menarche, blood pressure and anthropometry showed positive associations with age at menopause and the strength of the associations differed between urban and rural regions only with anthropometric variables. Current BMI, BFP, WC and HC all increased approximately linearly with increasing age at menopause by 0.4 [0.03] kg/m^2, 0.7 [0.06] %, 0.9 [0.07] cm and 0.8 [0.05] cm per 10 years later menopause respectively ($p<0.0001$ for all: Table 3, Figures 6a-f), with rural women showing associations up to twice as strong as those seen in urban women ($p<0.008$ for all: Table 3). In rural women, the association of WC with age at menopause was again twice as strong (0.6cm versus 1.2cm per 10 years later menopause, $p<0.0001$) whereas the association of HC with age at menopause was only slightly stronger (0.8cm versus 0.7cm per 10 years later menopause, $p=0.008$: Table 3) compared to urban women. As a result of both WC and HC increasing similarly with age at menopause, WHR showed no significant association in urban women ($p=0.45$: Table 3). In rural women, the increase in WC was greater than the increase in HC leading to a significant but weak association with WHR ($p<0.0001$: Table 3). Notably, the strength of the positive associations between age at menopause and all anthropometric variables was only quarter of the strength of the inverse associations with age at menarche (Tables 2 -3).

Again in contrast to their association with age at menarche, blood pressure showed positive associations with age at menopause with no regional differences in the strength of the associations. Overall, mean SBP adjusted for area and year of birth increased linearly by 1.2 [0.17] mmHg per 10 years later menopause ($p<0.0001$: Table 3, Figure 7a), which was attenuated by half to 0.6 [0.17] mmHg when adjusted for current BMI, but still remained significant ($p=0.0002$: Table 3, Figure 7b). Similarly, mean DBP adjusted for area and year of birth increased linearly by 0.4 [0.08] mmHg per 10 years later menopause ($p<0.0001$: Table 3, Figure 7c), which was only marginally significant after being attenuated by half to 0.2 [0.08] mmHg when also adjusted for current BMI ($p=0.03$: Table 3, Figure 7d).

9.2 Discussion

The apparent changes in blood pressure and anthropometry with year of birth varied from linear trends for SBP and standing height to inverted U-shaped trends for all other variables, which were not consistent in magnitude or pattern within either urban or rural areas. Apart from height, which showed a real and important increasing secular trend, the trends in all other physical characteristics largely reflect age-related changes.

Blood pressure and anthropometry showed significant inverse associations with age at menarche and significant positive associations with age at menopause, all of which were up to twice as strong in rural women. However, the associations with blood pressure were mostly attenuated following adjustment for current BMI to marginal or no significance in urban women but remained significant in rural women. Age at menarche was more strongly associated with current BMI than with BMI at age 25, and up to four times more strongly associated with these adult CVD risk factors compared to age at menopause.

9.2.1 Secular trends of physical characteristics

As already suggested, the apparent changes in blood pressure with year of birth most likely reflect the expected age-related changes in these factors (see Baseline Description: Results) although a real secular trend given the overall changes in blood pressure and in anthropometry cannot be excluded. By contrast, the increasing secular trend in height suggests that there have been major nutritional improvements at the population level throughout China without any long-term impact of the Great Chinese Famine whether women experienced famine at birth (refuting the Barker hypothesis) or at any later time during their growth. The secular trends in anthropometry show that despite an initial period of increase mirroring the secular trend in height, there has been a steady decline for all women born from 1960 onwards. It is difficult to separate fully the effect of changes in nutrition and diet at the population level from age-related changes in anthropometry; however, it is likely that these results indicate overall nutritional improvements with a possible greater concern about obesity and desire for healthier lifestyles among the younger women. Although CKB women are not considered overweight or obese by conventional standards [200], using proposed cut-offs for Chinese adults of BMI >24kg/m^2 and WC >80cm [201, 202] indicates that urban women born prior to 1960 may be at higher risk for complications of overweight and obesity.

9.2.2 Association of blood pressure and anthropometry with age at menarche

There is consistent evidence from developed countries that age at menarche is inversely associated with BMI, but less is known about its association with other anthropometric measures or blood pressure, particularly following adjustment for BMI in the latter case (see Literature Review: Reproductive factors, anthropometry and blood pressure). In this study, age at menarche was also significantly inversely associated with both blood pressure and anthropometry, although the effects seemed to be primarily mediated through the inverse association between age at menarche and current BMI. However, the strength of the associations in CKB women were comparatively weaker than other somewhat smaller studies in American, British and Chinese populations [105, 163-176, 203], even prior to adjustment for BMI. Given the good reproducibility of both age at menarche and the physical characteristics of the CKB women (see Data Quality: Results), it is unlikely that these associations have been greatly attenuated towards the null by the random measurement error resulting from poor recall. It is therefore possible that age at menarche has a weaker relationship with these factors in a Chinese population.

As there were significant regional differences in age at menarche, blood pressure and anthropometry, the regional variations seen in these associations were not unexpected. All associations were stronger in rural women who, on average, had a later menarche and lower blood pressure and were thinner (see Baseline Description: Results). For example, the association between age at menarche and blood pressure was entirely accounted for by current BMI in urban women but was still significant after adjustment for current BMI in rural women. This suggests that there may be environmental exposures linked to place of residence – such as diet and physical activity – not accounted for in these analyses that influence the strength of the association.

Notably the association of age at menarche with current BMI was twice as strong as that with BMI at age 25. Although this pattern is suggested by current evidence on the association of age at menarche with BMI at various ages (see Literature Review: Reproductive factors, anthropometry and blood pressure), this is the first large study to look at the association with BMI at different ages in the same group of women. BMI tracks from childhood through to adulthood and, in other studies, both childhood and adult BMI were associated with age at menarche, although the association with adult BMI became non-significant after adjustment for adolescent BMI (see Literature Review: Reproductive factors, anthropometry and blood pressure). Thus differences in age at menarche (which is strongly correlated with adolescent BMI) may represent different growth trajectories in childhood that continue to diverge in adulthood producing inverse associations between age at menarche and adult BMI that increase in strength with age.

9.2.3 Association of blood pressure and anthropometry with age at menopause

There is very limited and inconsistent information to date on the association between age at menopause and blood pressure and anthropometry (see Literature Review: Reproductive factors, anthropometry and blood pressure). The changes in blood pressure and anthropometry per 10 years later menopause were small but significant in CKB women. These positive associations contrast with 2 studies of 2588 Norwegian [177] and 1022 Japanese women [178] that failed to find any association, probably because they were underpowered to detect weak associations similar to those seen among CKB women. Due to the very limited literature from large studies on this topic, it is not possible to comment on how the strength of these associations would compare to other populations, but, given the size of this study and the good reproducibility of both age at menopause and physical characteristics in CKB women, it is highly likely that the associations observed are real.

Although most of the association between age at menopause and DBP was accounted for by current BMI, the association with SBP still remained significant after adjustment. This may be because age at menopause has a small effect on SBP via another mechanism or because DBP is measured less reliably than SBP (see Data Quality: Results) producing a weaker association with age at menopause which is attenuated to a greater degree since BMI is measured very reliably (see Data Quality: Results). Despite urban women having a significantly later age at menopause and a lower SBP and DBP for all year-of-birth cohorts, no significant regional differences in these associations were seen. By contrast, the association between age at menopause and anthropometry was significantly stronger in rural women despite similar reproducibility of anthropometric variables in both regions. As with age at menarche, these associations may be further affected by environmental exposures such as diet linked to place of residence.

9.2.4 Comparison of the associations of blood pressure and anthropometry with age at menarche and age at menopause

As there is only a weak U-shaped association between age at menarche and age at menopause, it is likely that both factors are independently associated with adult blood pressure and anthropometry, although, unexpectedly, the association with age at menarche was up to four times stronger than that with age at menopause. Furthermore, the only known correlates of age at menarche and menopause in this study that overlap are region of residence, education and occupation, but as these probably represent environmental exposures rather than being determinants themselves, they are unlikely to act as significant confounders.

The majority of the association of age at menarche and menopause with blood pressure was accounted for by the association with current BMI, which suggests that these reproductive factors have little effect on blood pressure independent of their association with BMI. Both later age at menarche and earlier age at menopause were associated with lower blood pressure and healthier anthropometry which implies that a shorter reproductive window may be linked to a better cardiovascular risk profile. However, it is important to note that all the associations seen in this thesis are weak in comparison to the effect of diet, physical activity and genetic determinants on blood pressure [204, 205] and anthropometry [206-208], notwithstanding the strong association between BMI and blood pressure as well [209, 210]. CKB is the largest study to date to have examined these associations in a Chinese population and has sufficient power to detect small but significant associations between reproductive factors and CVD risk factors. However, it remains to be determined whether these associations translate into significant differences in CVD incidence among CKB women.

9.3 Conclusion

Secular trends of physical characteristics indicate long-term nutritional improvements at the population level with no major disruptions due to the Great Chinese Famine. Although only preliminary analyses were done, age at menarche showed inverse associations with blood pressure and anthropometry that were weaker than those seen in other populations but up to four times stronger than the positive associations between these factors and age at menopause. However, the association of blood pressure with each reproductive factor seems to be largely dependent on anthropometry. Regional differences suggest that environmental exposures linked to place of residence not accounted for in these analyses may influence the strength of the association between reproductive factors and anthropometry – these possible confounders will have to be accounted for in future analyses on the relationship of reproductive history with CVD. The large population in this study permits detection of small but significant changes in CVD risk factors with age at menarche and menopause, which suggest that a shorter reproductive window may be linked to a lower risk of CVD. However, it is uncertain whether this will impact significantly on CVD incidence among CKB women.

Table 1. Models for the association between year of birth and physical characteristics

Physical characteristic	Region	Year-of-birth cohort	Change[1] (SE) per 10 year-of-birth cohorts	F-value for interaction between year of birth and region[2]	p-value
SBP (mmHg)	Urban	1930-74	-8.8 (0.05)		
	Rural	1930-74	-8.4 (0.05)	1930-74: 27	<0.0001
DBP (mmHG)	Urban	1930-50	1.8 (0.09)		
		>1950	-3.8 (0.06)		
	Rural	1930-50	1.4 (0.09)	1930-50: 13	0.0004
		>1950	-2.8 (0.05)	>1950: 154	<0.0001
Height (cm)	Urban	1930-74	1.8 (0.01)		
	Rural	1930-74	1.8 (0.01)	1930-74: 23	<0.0001
BMI (kg/m²)	Urban	1930-50	0.3 (0.03)		
		>1950	-1.1 (0.02)		
	Rural	1930-60	0.6 (0.01)	1930-50: 159	<0.0001
		>1960	-1.2 (0.04)	>1960: 12	0.0004
Weight (kg)	Urban	1930-50	2.3 (0.07)		
		>1950	-1.8 (0.05)		
	Rural	1930-60	2.7 (0.04)	1930-50: 103	<0.0001
		>1960	-2.7 (0.11)	>1960: 7	0.007
BFP (%)	Urban	1930-50	0.7 (0.06)		
		>1950	-2.0 (0.04)		
	Rural	1930-60	1.2 (0.03)	1930-50: 122	<0.0001
		>1960	-1.8 (0.08)	>1960: 18	<0.0001
WC (cm)	Urban	1930-40	0.9 (0.26)		
		>1940	-3.3 (0.03)		
	Rural	1930-50	1.2 (0.08)	1930-40: 1	0.26
		>1950	-2.4 (0.04)	>1950: 556	<0.0001
HC (cm)	Urban	1930-50	0.6 (0.05)		
		>1950	-1.1 (0.03)		
	Rural	1930-60	1.0 (0.03)	1930-50: 87	<0.0001
		>1960	-1.8 (0.08)	>1960: 1	0.37
WHR	Urban	1930-40	0.00 (0.002)		
		>1940	-0.03 (0.000)		
	Rural	1930-50	0.00 (0.001)	1930-40: 1	0.30
		>1950	-0.02 (0.000)	>1950: 403	<0.0001

[1] Adjusted for area within region and also for interaction between year-of-birth and region

[2] Values given for year-of-birth cohorts that have the same direction of association in both urban and rural women

Table 2. Models for the association between age at menarche and physical characteristics

Physical characteristic	Region	Change[1] (SE) per 10 year increase in age at menarche	p-value	F-value for interaction between age at menarche and region	p-value
Anthropometry					
Current BMI (kg/m²)	Urban	-1.8 (0.05)	<0.0001		
	Rural	-2.2 (0.04)	<0.0001		
	Overall	-2.0 (0.03)	<0.0001	543	<0.0001
BMI at age 25 (kg/m²)	Urban	-0.5 (0.04)	<0.0001		
	Rural	-0.9 (0.04)	<0.0001		
	Overall	-0.7 (0.03)	<0.0001	180	<0.0001
BFP (%)	Urban	-2.8 (0.10)	<0.0001		
	Rural	-4.0 (0.09)	<0.0001		
	Overall	-3.4 (0.07)	<0.0001	631	<0.0001
WC (cm)	Urban	-3.0 (0.13)	<0.0001		
	Rural	-4.8 (0.12)	<0.0001		
	Overall	-3.8 (0.09)	<0.0001	667	<0.0001
HC (cm)	Urban	-2.9 (0.09)	<0.0001		
	Rural	-3.0 (0.08)	<0.0001		
	Overall	-2.8 (0.06)	<0.0001	130	<0.0001
WHR	Urban	-0.01 (0.001)	<0.0001		
	Rural	-0.02 (0.001)	<0.0001		
	Overall	-0.02 (0.001)	<0.0001	746	<0.0001
Blood pressure					
SBP (mmHg)	Urban	-3.2 (0.28)	<0.0001		
	Rural	-6.2 (0.27)	<0.0001		
	Overall	-4.8 (0.20)	<0.0001	74	<0.0001
Also adjusted for BMI	Urban	-0.5 (0.28)	0.05		
	Rural	-3.1 (0.26)	<0.0001		
	Overall	-2.0 (0.19)	<0.0001	9	0.003
DBP (mmHg)	Urban	-1.6 (0.15)	<0.0001		
	Rural	-2.9 (0.14)	<0.0001		
	Overall	-2.3 (0.11)	<0.0001	135	<0.0001
Also adjusted for BMI	Urban	-0.3 (0.15)	0.07		
	Rural	-1.3 (0.14)	<0.0001		
	Overall	-0.9 (0.10)	<0.0001	42	<0.0001

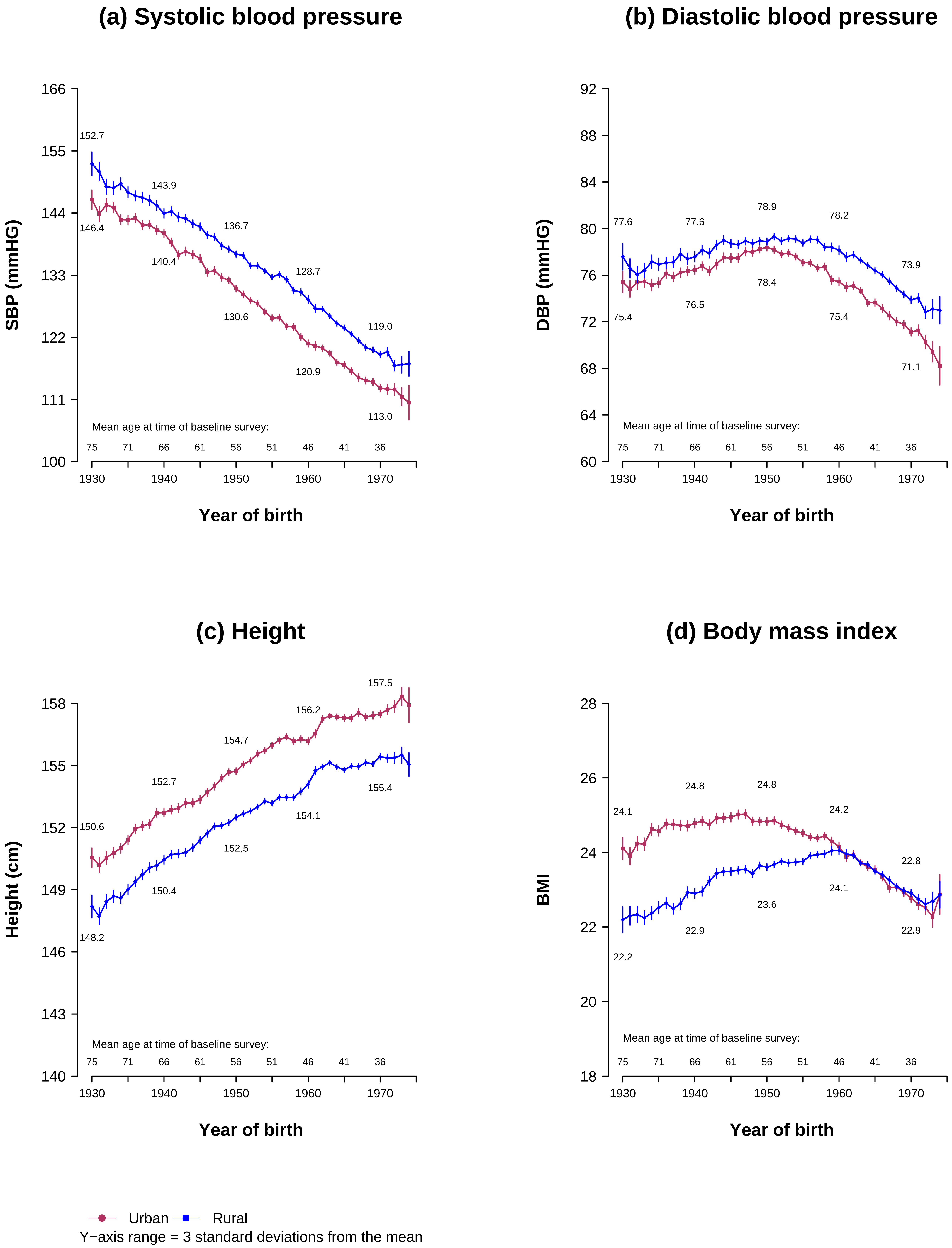
[1] Adjusted for year of birth, area within region and interaction between age at menarche and region

Table 3. Models for the association between age at menopause and physical characteristics

Physical characteristic	Region	Change[1] (SE) per 10 year increase in age at menopause	p-value	F-value for interaction between age at menopause and region	p-value
Anthropometry					
Current BMI (kg/m²)	Urban	0.3 (0.04)	<0.0001		
	Rural	0.5 (0.04)	<0.0001		
	Overall	0.4 (0.03)	<0.0001	13	0.0003
BFP (%)	Urban	0.5 (0.08)	<0.0001		
	Rural	0.8 (0.08)	<0.0001		
	Overall	0.7 (0.06)	<0.0001	12	0.0004
WC (cm)	Urban	0.6 (0.10)	<0.0001		
	Rural	1.2 (0.10)	<0.0001		
	Overall	0.9 (0.07)	<0.0001	29	<0.0001
HC (cm)	Urban	0.7 (0.07)	<0.0001		
	Rural	0.8 (0.07)	<0.0001		
	Overall	0.8 (0.05)	<0.0001	7	0.008
WHR	Urban	0.00 (0.001)	0.45		
	Rural	0.01 (0.001)	<0.0001		
	Overall	0.00 (0.001)	<0.0001	36	<0.0001
Blood pressure					
SBP (mmHg)	Urban	1.2 (0.24)	<0.0001		
	Rural	1.3 (0.24)	<0.0001		
	Overall	1.2 (0.17)	<0.0001	0	0.64
Also adjusted for BMI	Urban	0.7 (0.24)	0.002		
	Rural	0.5 (0.23)	0.02		
	Overall	0.6 (0.17)	0.0002	0	0.70
DBP (mmHg)	Urban	0.4 (0.12)	0.0002		
	Rural	0.4 (0.12)	0.0002		
	Overall	0.4 (0.08)	<0.0001	0	0.87
Also adjusted for BMI	Urban	0.2 (0.11)	0.06		
	Rural	0.1 (0.11)	0.25		
	Overall	0.2 (0.08)	0.03	1	0.37

[1] Adjusted for year of birth, area within region and interaction between age at menopause and region

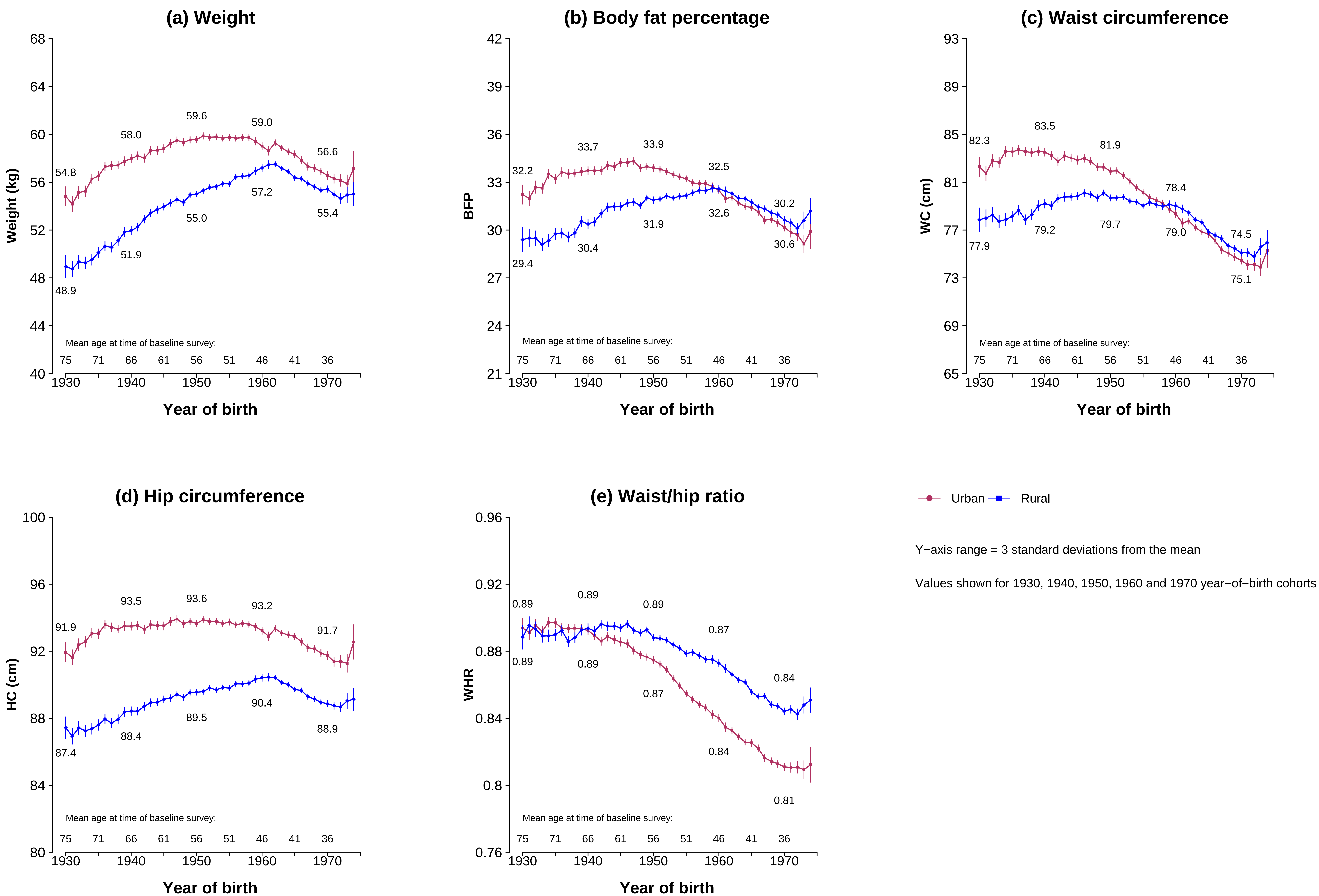
Figure 1. Area−adjusted secular trends of physical characteristics in 302 180 women, by urban and rural residence



Y−axis range = 3 standard deviations from the mean

Values shown for 1930, 1940, 1950, 1960 and 1970 year−of−birth cohorts

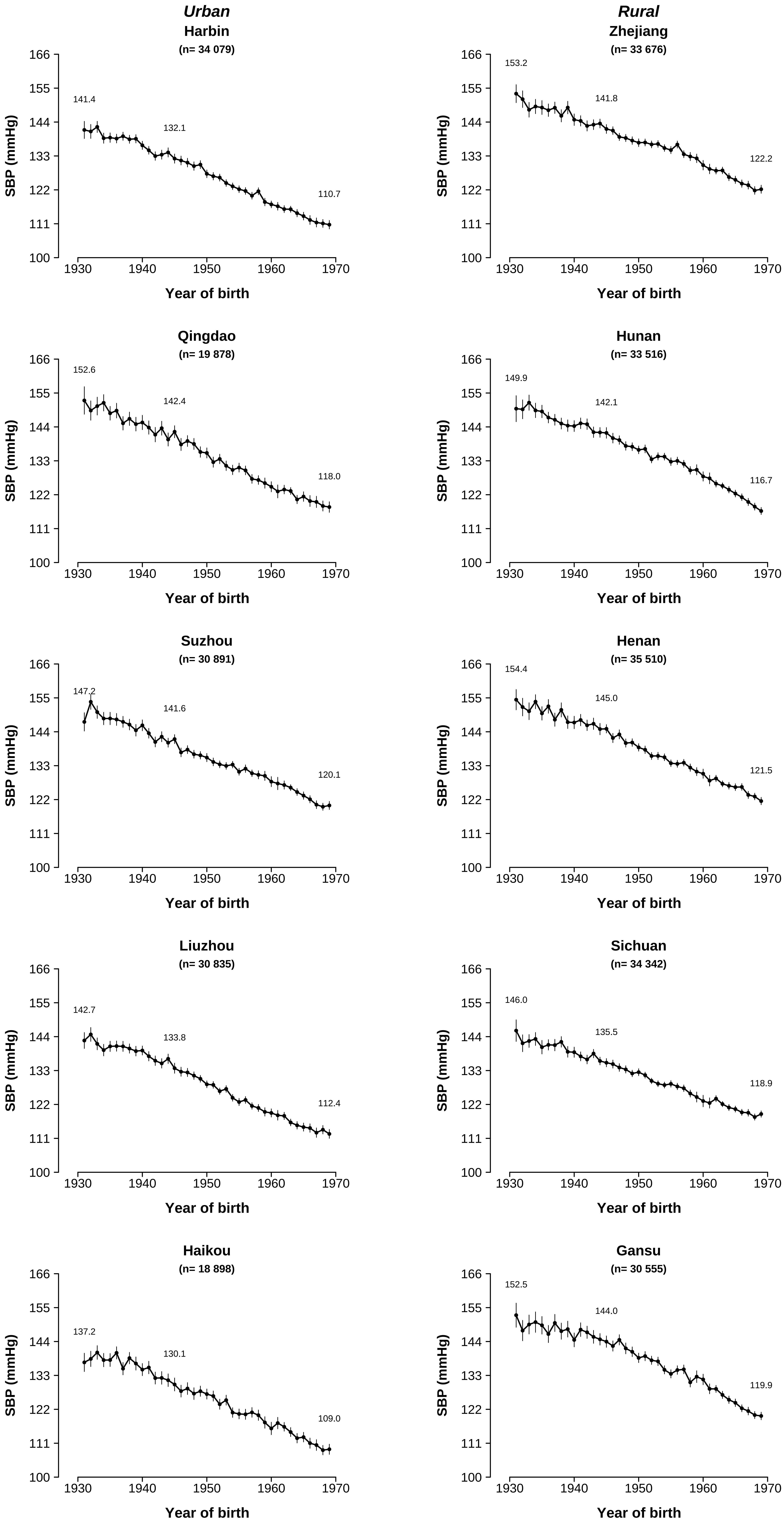
Figure 2. Area−adjusted secular trends of anthropometric measurements in 302 180 women, by urban and rural residence



Y−axis range = 3 standard deviations from the mean

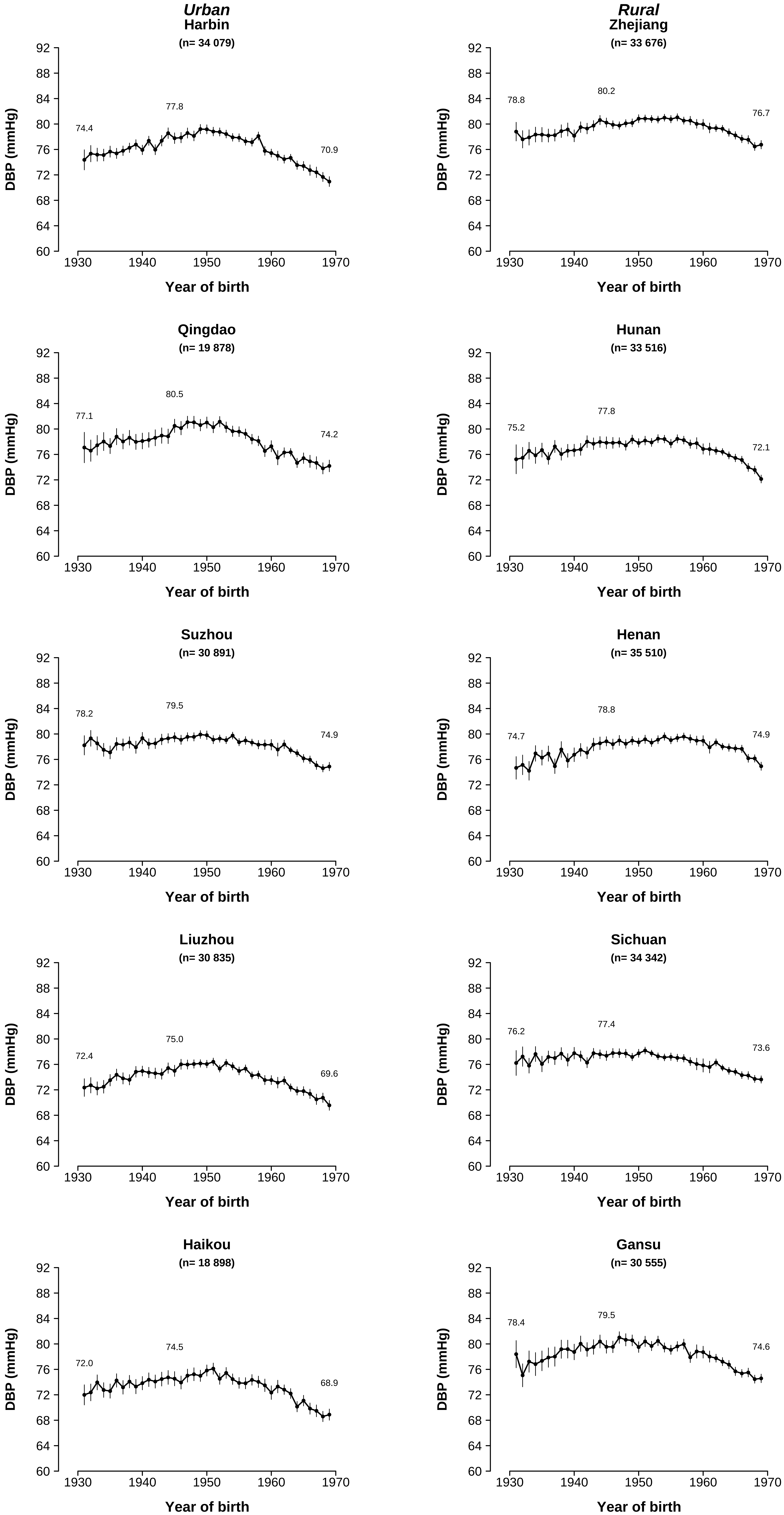
Values shown for 1930, 1940, 1950, 1960 and 1970 year−of−birth cohorts

Figure 3a. Mean systolic blood pressure versus year of birth (1931−69) within each area



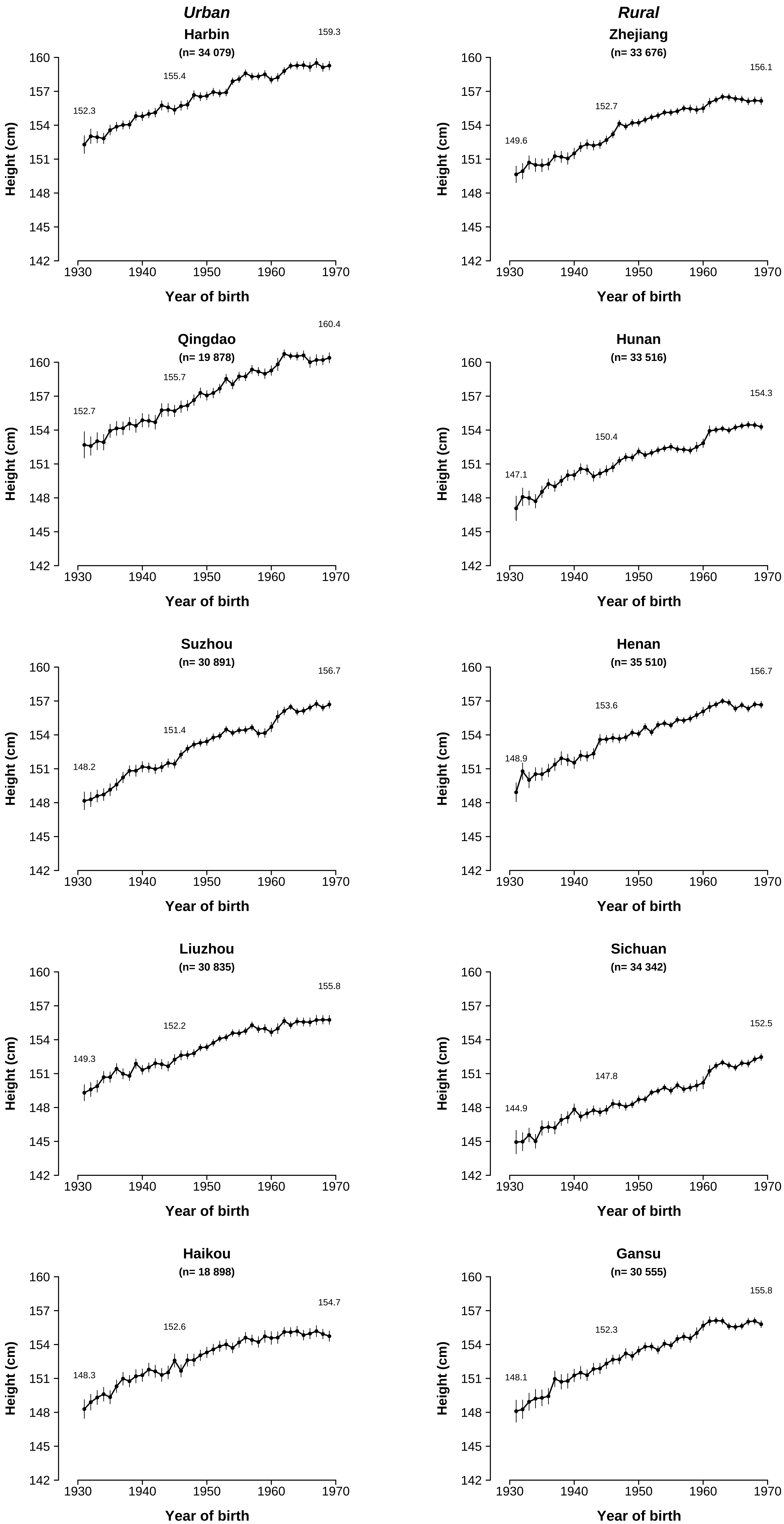
Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

Figure 3b. Mean diastolic blood pressure versus year of birth (1931−69) within each area



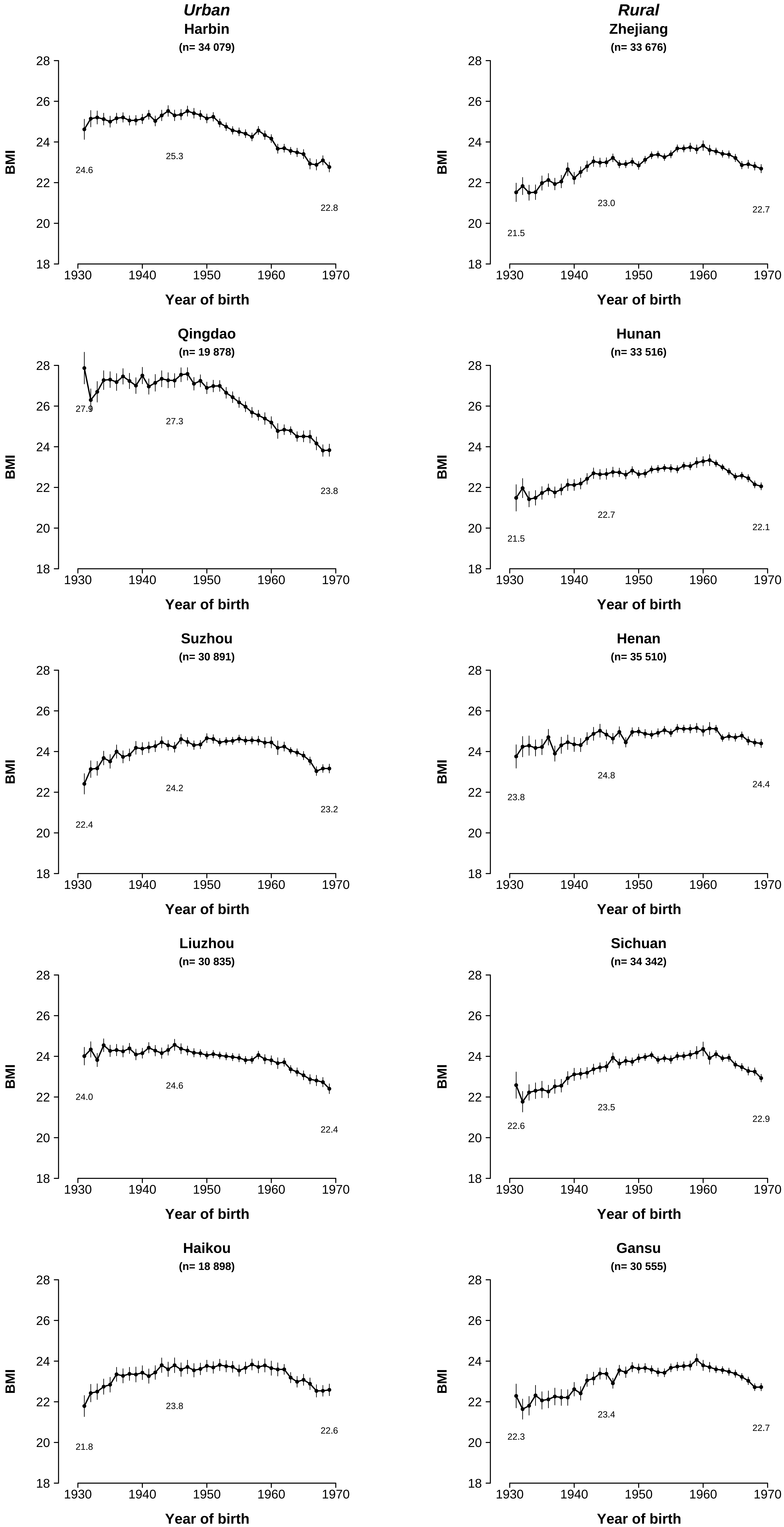
Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

Figure 3c. Mean standing height versus year of birth (1931−69) within each area



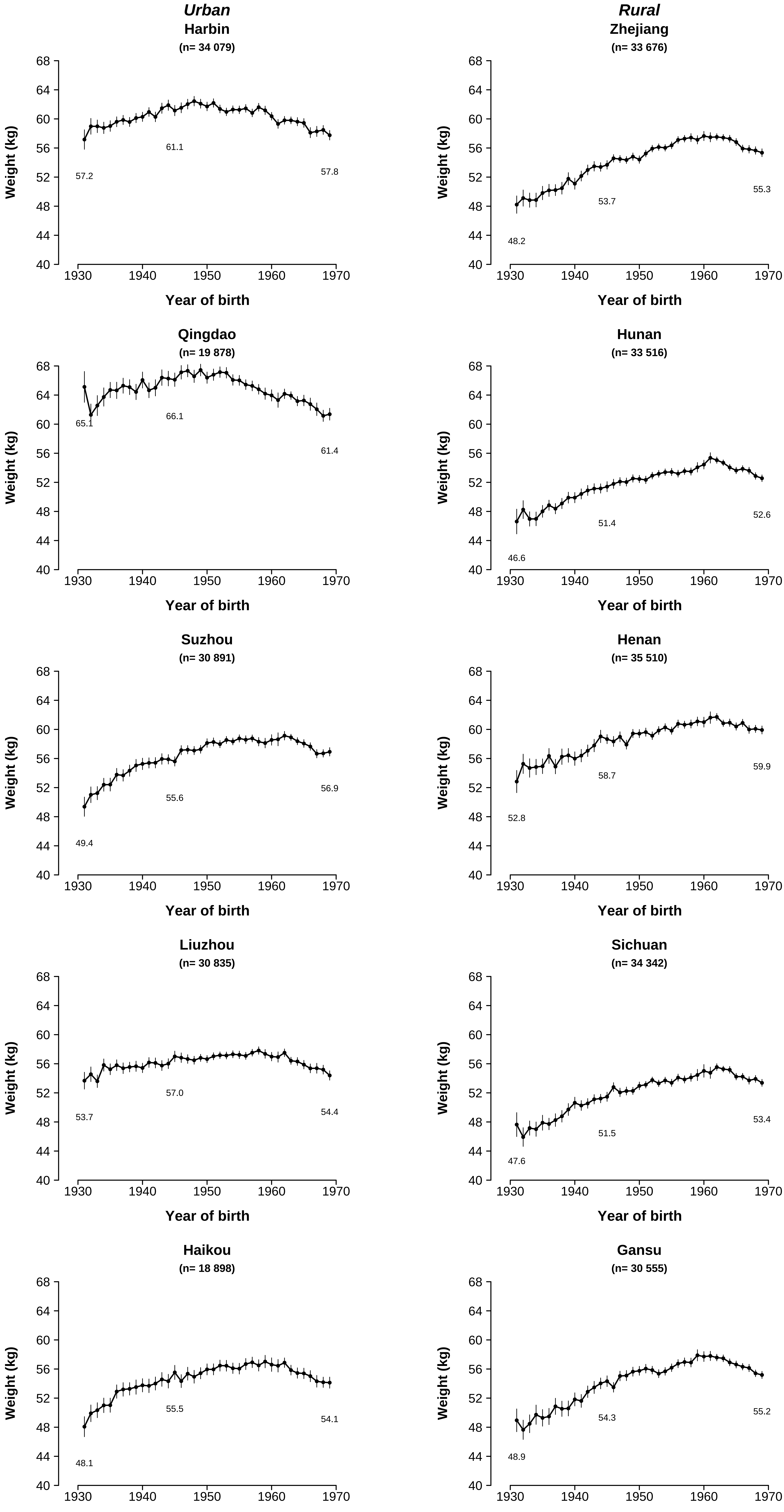
Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

Figure 3d. Mean body mass index versus year of birth (1931−69) within each area



Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

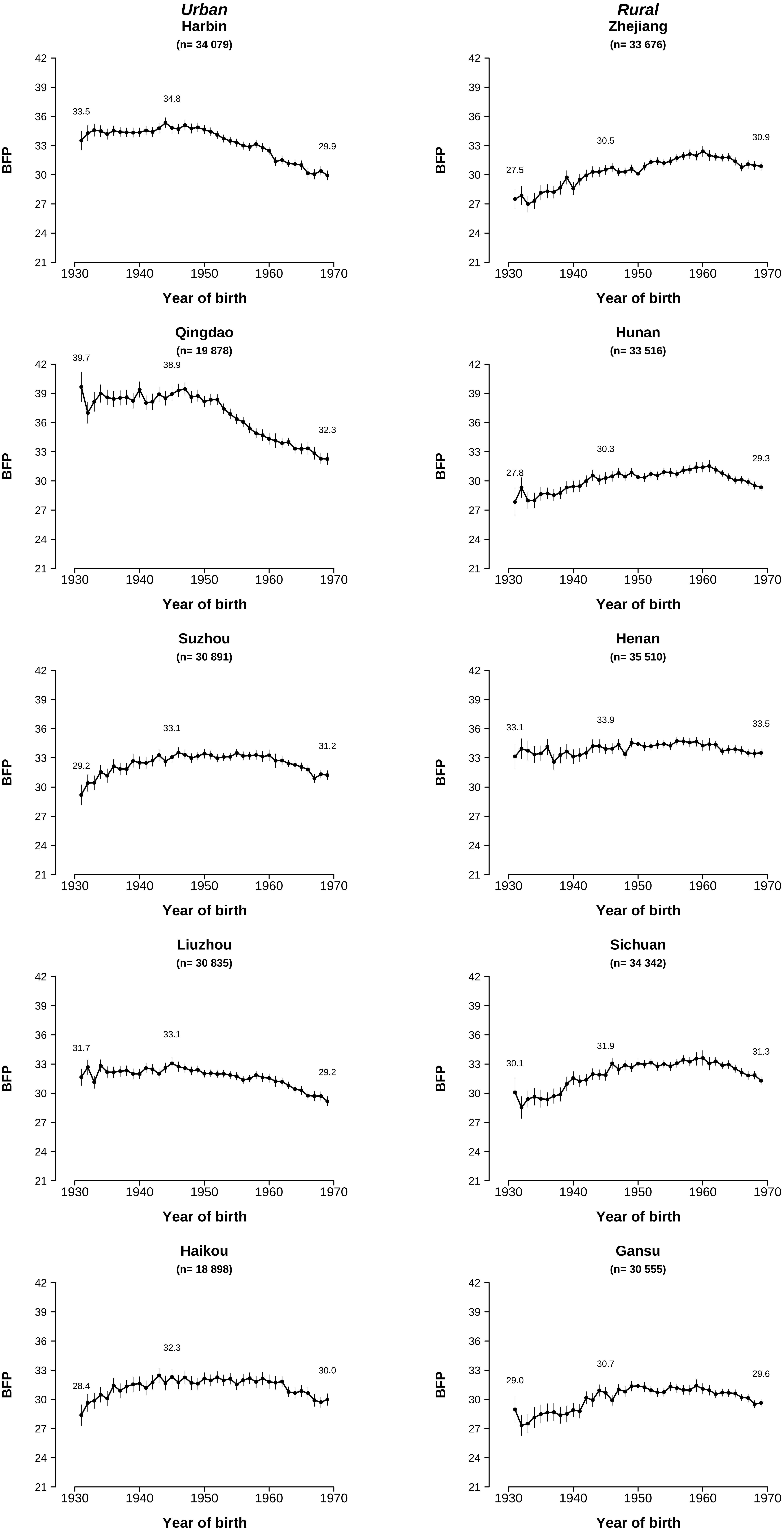
Figure 3e. Mean weight versus year of birth (1931−69) within each area



Urban regions are ordered North to South and rural regions are ordered coastal to inland.

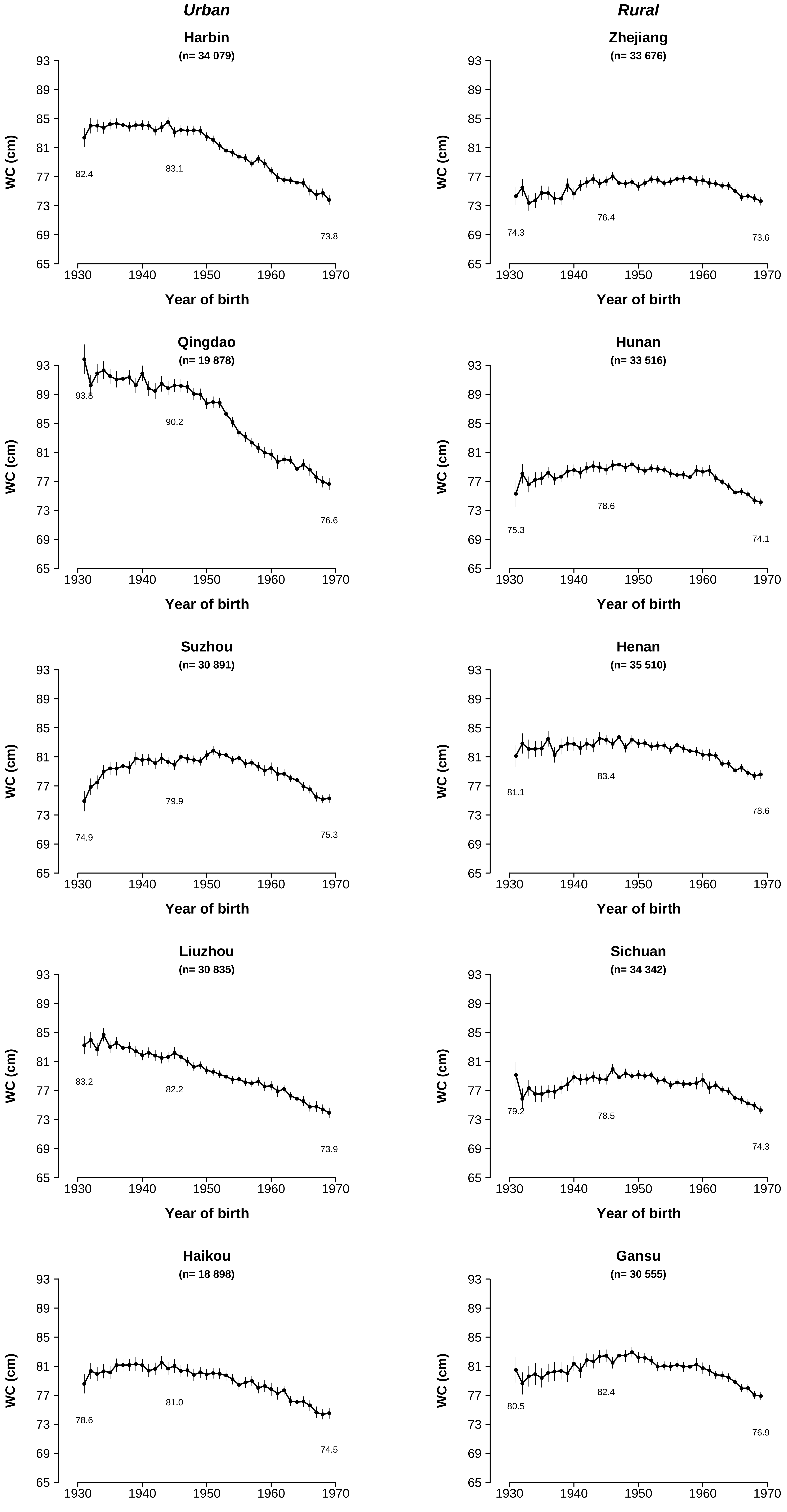
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

Figure 3f. Mean body fat percentage versus year of birth (1931−69) within each area



Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

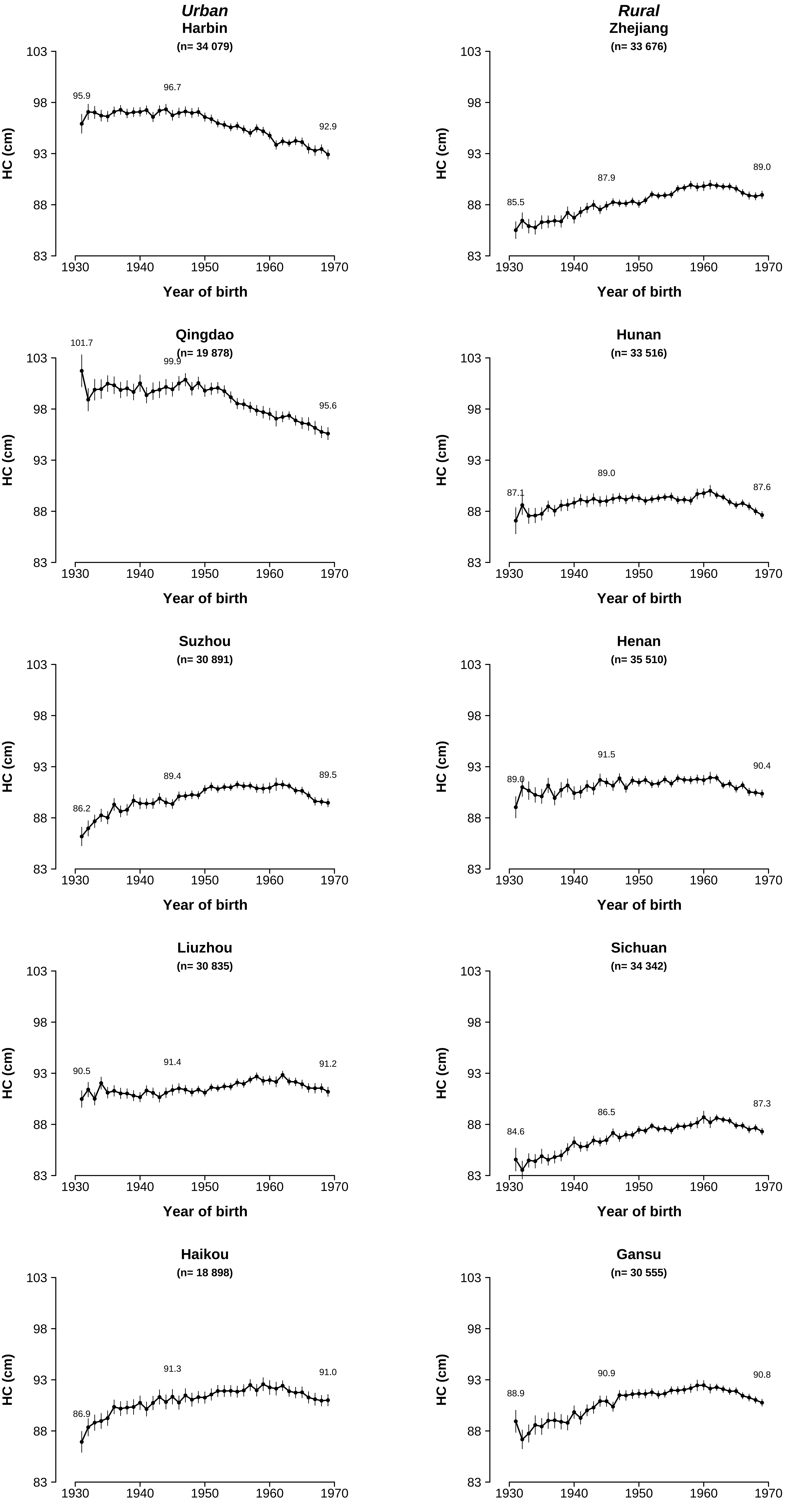
Figure 3g. Mean waist circumference versus year of birth (1931−69) within each area



Urban regions are ordered North to South and rural regions are ordered coastal to inland.

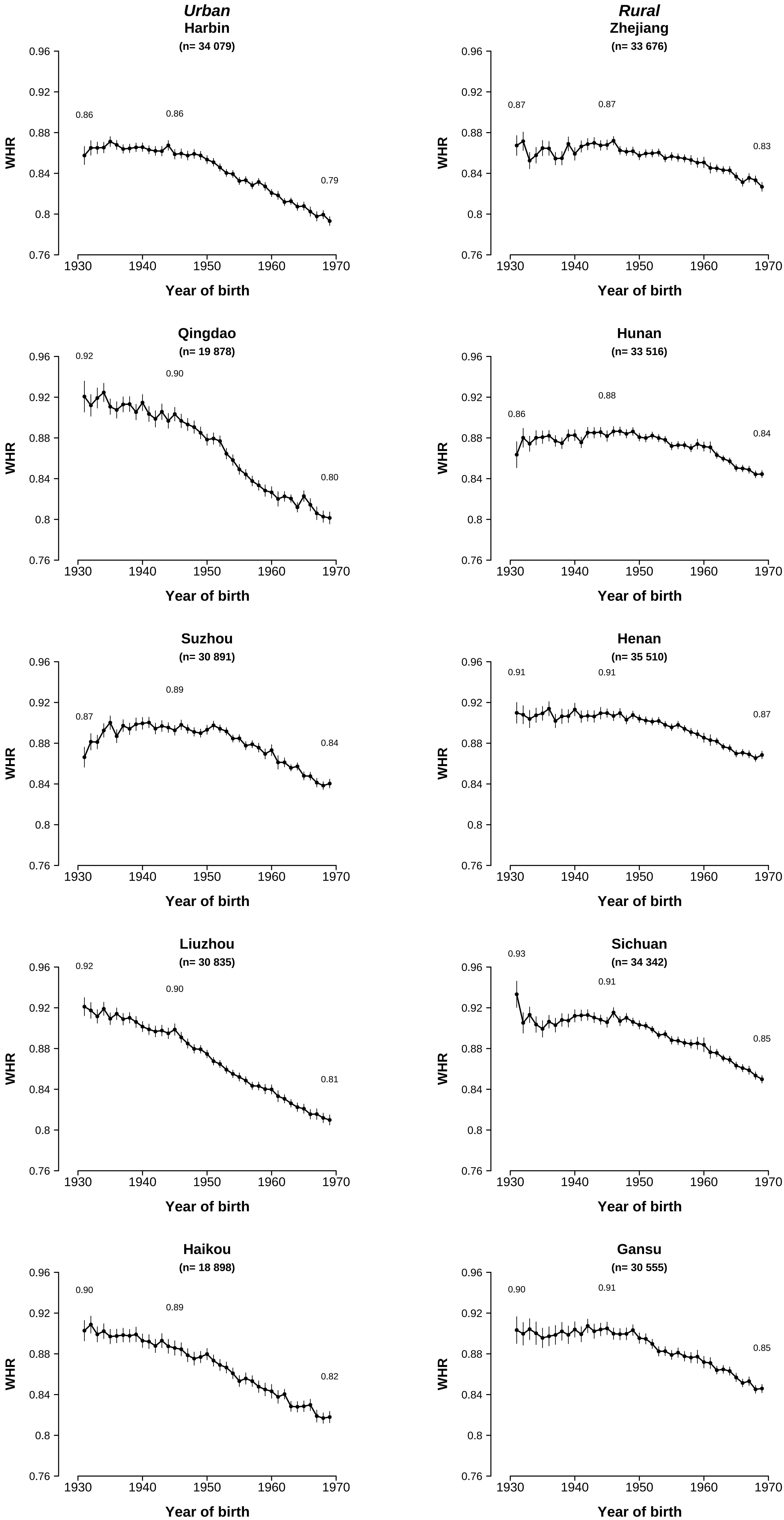
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

Figure 3h. Mean hip circumference versus year of birth (1931−69) within each area



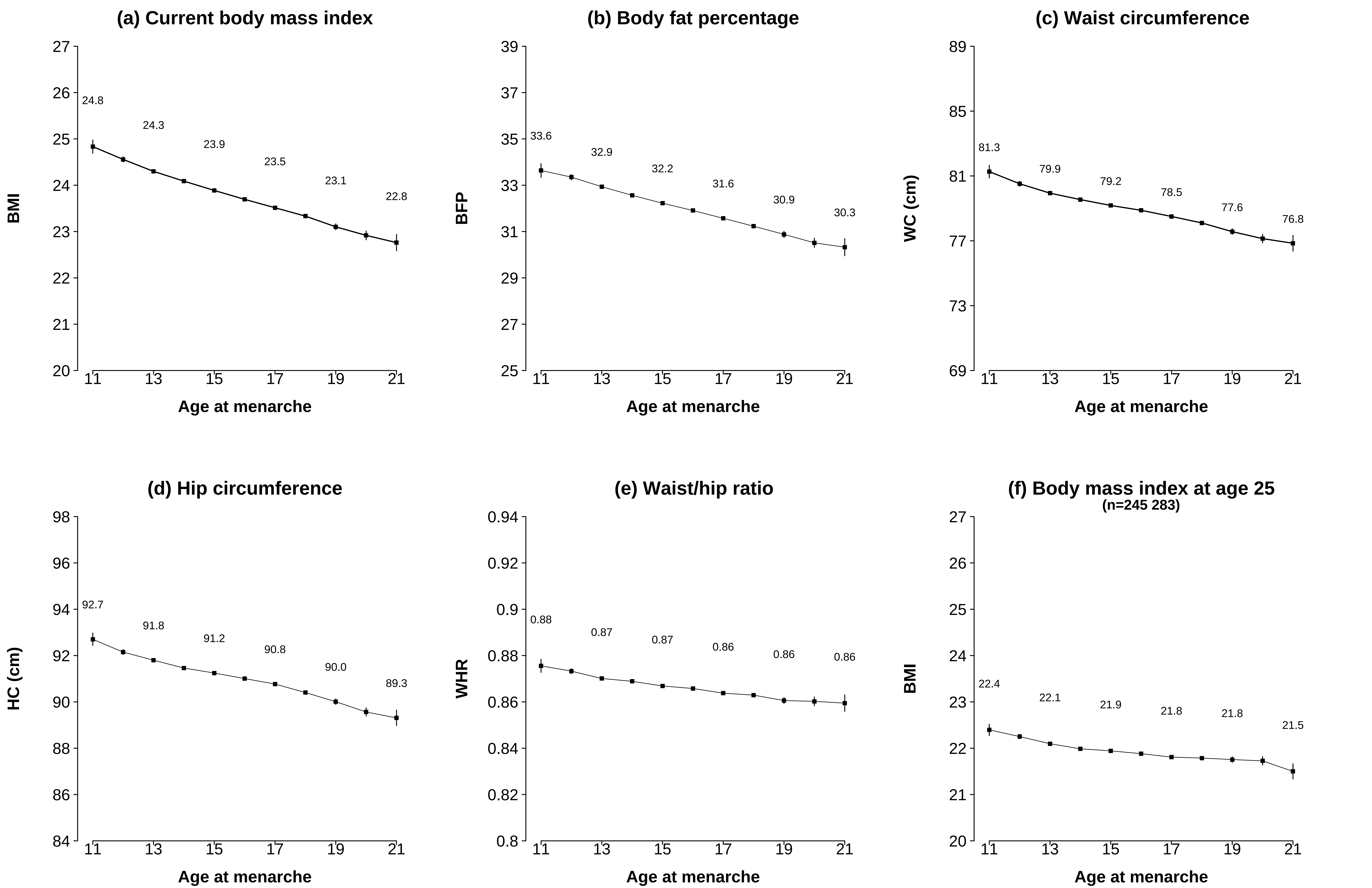
Y−axis range different from Figure 1b to accomodate range of regional means
Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

Figure 3i. Mean waist/hip ratio versus year of birth (1931−69) within each area



Urban regions are ordered North to South and rural regions are ordered coastal to inland.
Values shown for 1931, 1945 and 1969 year−of−birth cohorts.

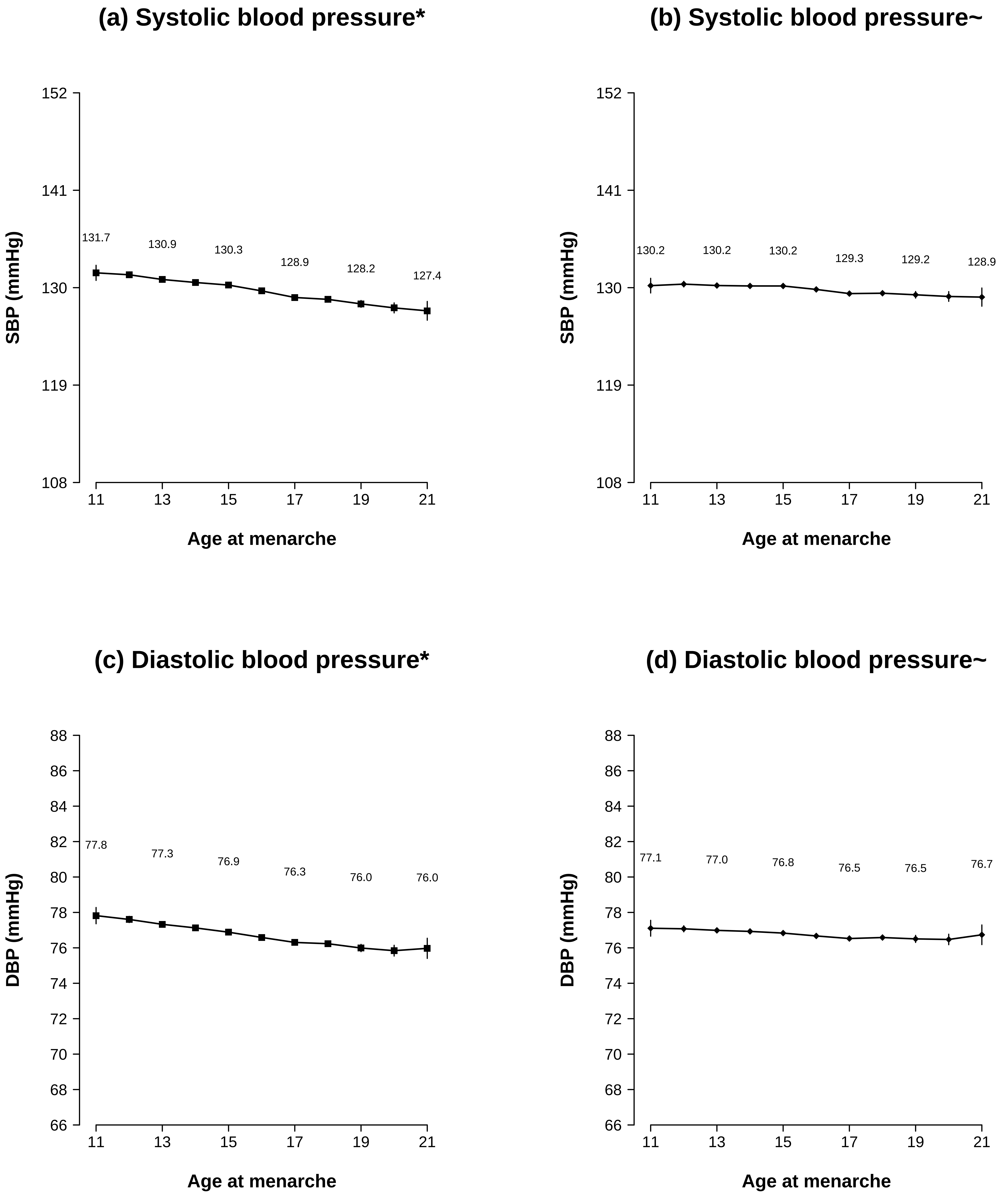
Figure 4. Adjusted mean* anthropometric measurements by age at menarche in 302 180 women



*Adjusted for area and year of birth
Y−axis range = 2 standard deviations from mean

Values shown where age at menarche = 11, 13, 15, 17, 19 and 21
Means shown for those ages at menarche with >1000 women

Figure 5. Adjusted mean blood pressure versus age at menarche in 302 180 women



Y−axis range = 2 standard deviations from the mean

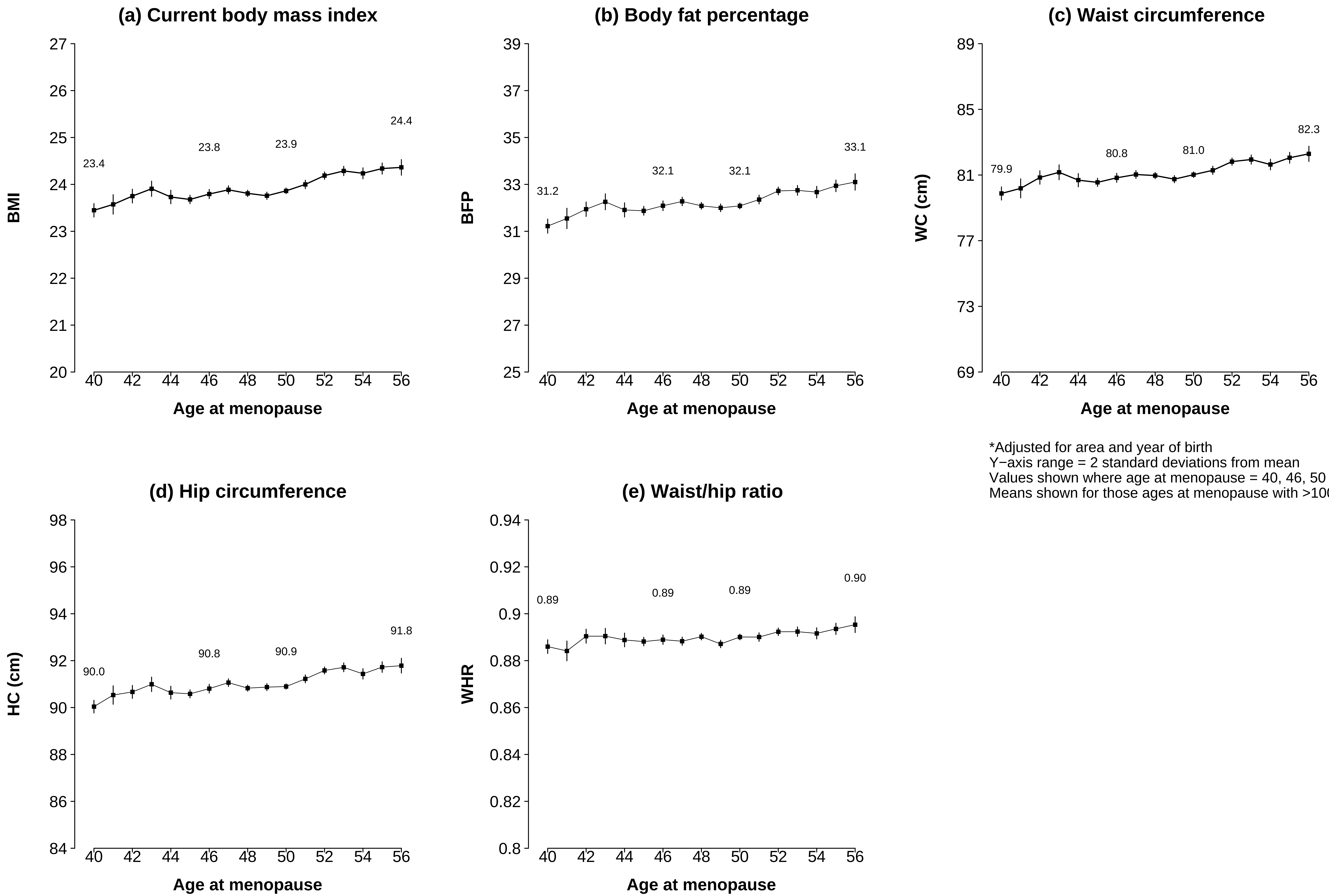
*Adjusted for area and year of birth

~Adjusted for area, year of birth and BMI

Values shown where age at menarche = 11, 13, 15, 17, 19 and 21

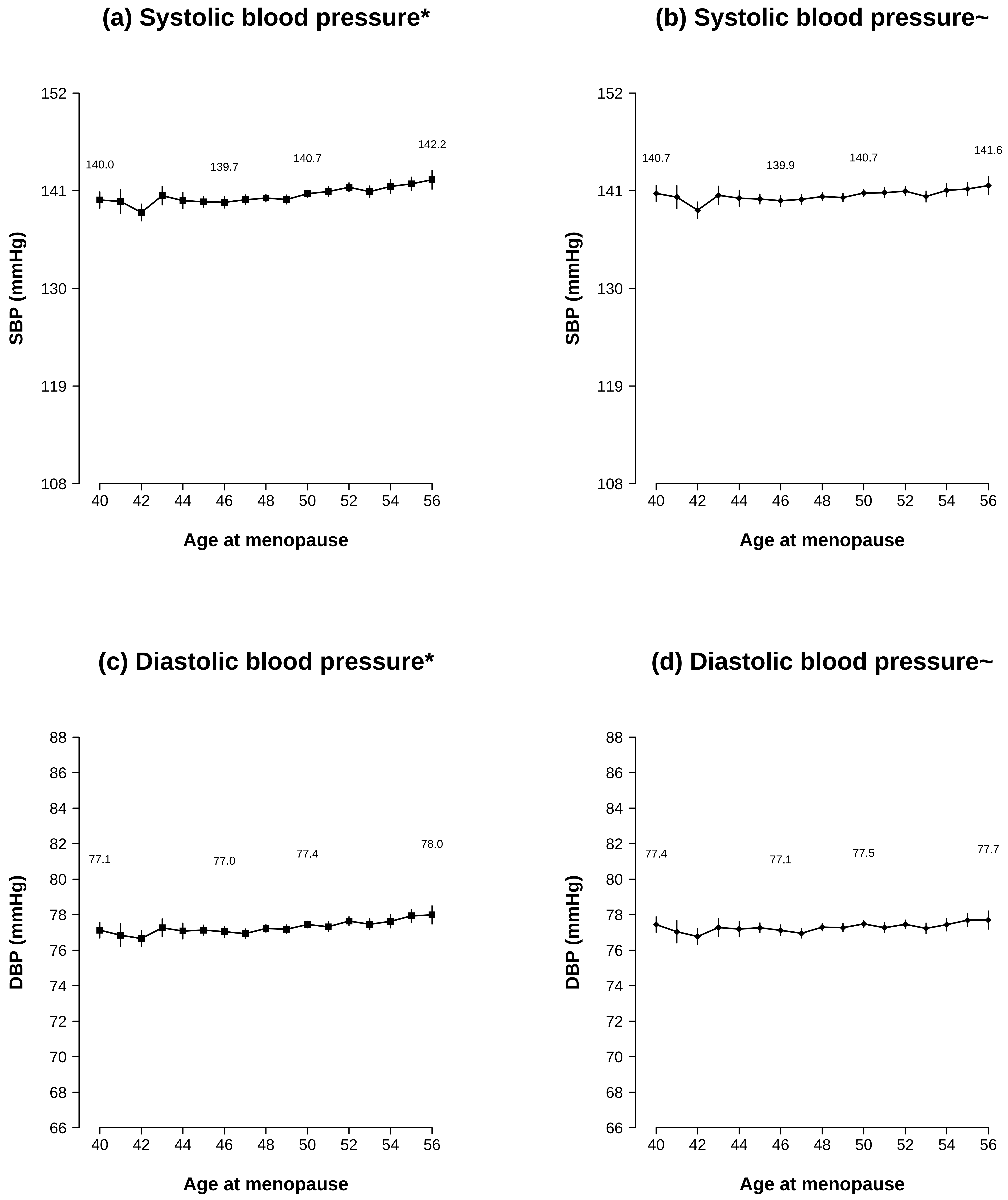
Means shown for those ages at menarche with >1000 women

Figure 6. Adjusted mean* anthropometric measurements versus age at menopause in 89 320 women



*Adjusted for area and year of birth
Y−axis range = 2 standard deviations from mean
Values shown where age at menopause = 40, 46, 50 and 56
Means shown for those ages at menopause with >1000 women

Figure 7. Adjusted mean blood pressure versus age at menopause in 89 320 women



Y−axis range = 2 standard deviations from the mean

*Adjusted for area and year of birth

~Adjusted for area, year of birth and BMI

Values shown where age at menopause = 40, 46, 50 and 56

Means shown for those ages at menopause with >1000 women

Chapter 10. Study summary and implications

10.1 Study summary

The China Kadoorie Biobank is a prospective cohort of 0.5 million men and women from 10 areas in China with a focus on chronic disease outcomes. In this study, 302 180 women born in 1930-74 from all 10 areas provided data on reproductive history as well as a range of other demographic, socioeconomic and behavioural factors. There was good reproducibility of most variables with the exception of OC use, number of still births, number of spontaneous abortions and famine exposure. This study population had a wide range of demographic, physical and reproductive characteristics that showed large differences with area, year of birth and SES. In all areas, there were important age-related trends in SBP and DBP, as well as a low prevalence of regular smoking, regular alcohol consumption and past or present OC use. The secular trends in height and anthropometry indicate long-term nutritional improvements at the population level with no major disruptions due to the Great Chinese Famine, which may have implications for the prevalence of obesity-related diseases in this population.

Among CKB women, mean age at menarche has decreased by approximately 2 years over 44 year-of-birth cohorts, most likely due to improvements in nutrition at the population level. Despite this trend, famine exposure was associated with approximately a 1 year delay in menarche among women experiencing puberty around the time of the Great Chinese Famine, although the effect size varied among study areas. More educated women had an earlier menarche and were also relatively protected against the effect of famine exposure. By contrast, there was only a very weak association between age at menarche and long-term childhood nutrition, as represented by adult height.

Among a subset of 89 320 women aged ≥57, age at menopause has steadily increased by 1.4 years over 21 year-of-birth cohorts and, unlike age at menarche, no major disruption of the secular trend coinciding with birth, puberty or any other major life event at the time of the Great Chinese Famine was seen. Age at menopause was significantly associated with several reproductive, socioeconomic and behavioural factors. Although current smokers and women with no formal schooling had menopause 6 months and 1 year earlier than their non-smoking and university-educated counterparts respectively, gravidity had by far the greatest effect: women with at least one pregnancy had menopause 2 years later than women who had never been pregnant.

Preliminary analyses showed inverse associations of age at menarche with blood pressure and anthropometry that were up to four times stronger than the positive associations between these factors and age at menopause; however, the associations with blood pressure were largely mediated by the association with adult BMI. The association of anthropometry with each reproductive factor is likely to be independent of each other given the very weak association between age at menarche and menopause in CKB women. Based on these results, it is possible that a shorter reproductive window may be linked to lower CVD risk in adulthood. Regional differences suggest that environmental exposures linked to place of residence not accounted for in these analyses may influence the strength of the association, and so further adjustment for possible confounders will have to be done in future analyses by CKB. In addition, there may be effects of age at menarche and menopause on blood-based CVD risk factors, such as cholesterol and its fractions that were not possible to assess in this study.

Due to its large size and detailed high-quality data, this study offers far greater insight on the secular trends of age at menarche and menopause in China over the last century, as well as their association with reproductive, behavioural, socioeconomic and famine exposure variables than has previously been possible. The large population in this study permits detection of small but significant changes in CVD risk factors with age at menarche and menopause, but it is uncertain whether the secular changes in age at menarche and menopause will impact significantly on CVD.

10.2 Strengths and limitations of this study

Although this thesis offers new information on the correlates of age at menarche and menopause in a large Chinese population and also suggests that reproductive history may have implications for the CVD risk profiles of these women, its strengths and limitations must nevertheless be considered.

CKB provides a wide range of data on a large number of Chinese women from 10 different areas which has permitted reliable analyses of the secular trends and correlates of two major reproductive factors, and also provided a starting point for the analysis of the association between reproductive history and CVD. A major strength of this study is the high overall quality of the data collected in CKB on demographic, reproductive and physical characteristics which showed generally good reproducibility (see Data Quality: Results) with very little missing information in the dataset as a whole.

However, CKB was not primarily designed as a reproductive health dataset. The questionnaire was designed to collect information on a large range of exposures relevant to chronic diseases within approximately one hour and so only a limited range of information on each set of exposures could be ascertained. Thus, in the case of reproductive health, CKB did not collect information on several important variables that may either influence other aspects of reproductive history or may be directly associated with chronic disease outcomes. These include use of hormonal contraception other than the OC pill, use of non-hormonal contraception such as intra-uterine contraceptive devices, indications for gynaecological surgery and HRT use or use of traditional Chinese medicine (which may themselves be oestrogenic) for relief of any symptoms relating to gynaecological conditions such as menopause. These gaps in data collection and their possible relevance to future analyses on reproductive health and its association with chronic diseases were brought to the attention of CKB's primary investigator, Prof Zhengming Chen, directly as a result of the work done in this thesis. Prof Chen has confirmed via personal communication that questions on these additional reproductive factors will be included in future surveys.

As with all observational studies, any associations found may be due to chance, bias or confounding. As the study involves a very large number of women, chance is unlikely to play a role but could arise in future when CKB analyses disease incidence data given the relatively short duration of follow up. An unusual element of selection bias may come from the inclusion of 'survivors' of the Great Chinese Famine, but as this is only a small proportion of the study population and no long-term effects from famine exposure are seen in any secular trend except age at menarche, this is unlikely to bias results. The main sources of bias would be responder bias and recall bias, both of which are probably very small in the present study. Responder bias was minimised by a concerted effort to recruit widely[4] and there was almost 100% completeness with data collection. In addition, there will be random sampling of non-responders in future CKB re-surveys to check if differences between participants and non-responders exist. Recall bias may be an issue with self-reported histories leading to measurement bias, but this can be reduced by the use of repeated measures, training of field staff, use of objective measures, and utilisation of more than one source of information where possible. The reproducibility of all variables in CKB will be monitored through the subsequent re-surveys where, as in the baseline

[4] All potentially eligible participants were identified through public registry records, and invitation letters with study information leaflets were delivered door-to-door by local community leaders or health workers following publicity campaigns.

survey, questionnaires will be administered in Mandarin by trained field workers with hard and soft limits for responses to maximise both validity and reproducibility. Although no medical records are available to check the validity of recalled reproductive history in CKB, other studies show that any misclassification is likely to be random [186, 188, 211] and would therefore tend to dilute an estimation of the true association between exposure and outcome [108]. In future, the quality of reproductive history data can also be checked by examining each factor's association with breast cancer, on which there is very good evidence.

A major challenge for cross-sectional analyses is the appropriate control of potential confounding factors. Measures taken in this study include using multivariate regression models with stepwise incorporation of potential confounders and application of specific exclusion criteria in each major set of analyses to avoid artefactual associations (e.g. restricting analyses of age at menopause to women aged ≥57 years to avoid an artefactual drop in mean age at menopause among later birth cohorts). Given the secular trends of reproductive factors in China and large variations between areas, all the main analyses were either adjusted for or stratified by area and year of birth as finely as the data would allow. Where attempts were made to adjust for possible confounders, no change in the results was seen in most cases. In some instances, adjustment for SES attenuated the strength of the associations, and it is possible that with more detailed information on SES the associations would be attenuated even further or even removed. Similarly, future detailed analyses on the association between reproductive history and CVD risk factors will require further adjustment for potential confounders than was possible in these preliminary analyses.

Another limitation of cross-sectional studies is that temporal relationships cannot be clearly established as in a prospective cohort study. Although it was possible in some cases to determine the sequence of events based on date of birth and reported age at the time of an event as well as external documentation of major events such as the Great Chinese Famine, all analyses have been treated as cross-sectional in this thesis. Provided that age at menarche is reliably reported, this study is suitable for investigating the effect of early/late menarche or menopause on adult CVD risk factors. However, the causes of early/late menarche or menopause could be better studied in a prospective cohort study where associations can be more rigorously examined and causal relationships can be established. In future, CKB will be able to investigate prospectively the effect of age at menopause on CVD incidence and compare these results with the findings on its association with CVD risk factors in this thesis.

As CKB is the largest study of its kind in China, another major strength is its power to detect small effects across a wide range of exposures that previous smaller studies may not have been able to do. Furthermore, although CKB was not designed to be representative of the Chinese population as a whole, it does nevertheless highlight important differences between urban and rural populations. While most of the effects seen in this thesis are statistically significant, they may not be clinically significant in terms of impact on disease incidence and prevalence. The 2 year difference in age at menarche between women born in 1930 and those born in 1974 (which is significant in itself) would still only result in 0.4 mmHg higher SBP and 0.4 kg/m^2 higher BMI. Similarly, the 1.4 year difference in age at menopause between women born in 1930 and those born in 1951 (which is also an appreciable change) would only result in 0.1mmHg and 0.1kg/m^2 lower SBP and BMI respectively. The strength of any observed associations must also be interpreted in the context of other known CVD risk factors – such as possible effects of age at menarche and menopause on blood-based CVD risk factors (e.g. cholesterol) – and the role of potential unknown or unmeasured confounders acknowledged. The small effect sizes presented in this thesis indicate that it is unlikely that reproductive factors will impact on CVD rates in China to the same extent as for example changes in smoking habits. However, given China's unique reproductive trends and CKB's extensive and high-quality data, CKB provides an excellent opportunity to examine the association of reproductive factors with CVD risk factors and subsequently CVD prevalence and incidence.

10.3 Implications of this study

As a starting point to tackling the controversy over the association of reproductive history with CVD, this thesis investigates secular trends and correlates of age at menarche and menopause as well as their associations with blood pressure and anthropometry as known CVD risk factors. The strength of the associations among CKB women was similar to or weaker than that seen in other populations where results in this study were consistent with existing evidence. In some instances, the findings of this study were not consistent with the frequently equivocal findings of other studies, including the Shanghai Women's Study – notably the only other large study of correlates of age at menopause in a Chinese population. This is most likely due to the inclusion of a much larger, more heterogeneous population with different patterns and range of exposures in CKB which permits reliable detection of small effects across finer categories of exposure. Thus, strong evidence is lacking, this thesis adds new knowledge on the correlates of age at menarche and age at menopause and in respect of the association of these reproductive factors with blood pressure and anthropometry among Chinese women born in the mid-20th century. Although CKB women have different patterns of exposure to most other populations studied so far, these findings may well be relevant specifically to other South-East Asian populations and developing countries, and more generally informative for associations where there is very limited evidence to date. However, this study is unable to establish causal relationships and cannot completely address the effects of residual confounding. Further examination of the relationship between reproductive history and CVD in CKB and other large, well-established prospective studies may add significantly to our understanding of the relevance of reproductive factors to women's health.

Chapter 11. Conclusion

The aims of this study were two-fold: firstly, to examine changes in and correlates of age at menarche and menopause, and secondly, to assess their associations with selected CVD risk factors among women in the China Kadoorie Biobank. While not intended to be representative, this study covers a wide range of exposures and outcomes in over 300 000 women from 10 different areas across China. It comprises extensive self-reported data with good reproducibility on reproductive, demographic and lifestyle factors as well as a range of physical measurements. China is particularly well-placed for studying the long-term effects of reproductive factors on women's health with its large population, relatively well-established health infrastructure, rapid changes in lifestyle, nutrition and reproductive behaviour (e.g. the introduction of a strict family planning policy), and increasing burden of chronic diseases such as CVD.

In this study, there were important secular trends in age at menarche, age at menopause, height and anthropometry that reflect rapid changes at the population level, with no long-term disruption in trends by the Great Chinese Famine except for a dramatic effect on age at menarche. In fact, famine exposure was the only factor to show a large effect on age at menarche; however, the results on other potential correlates need to be interpreted cautiously as CKB did not collect specific data on childhood factors. By comparison, a number of adult reproductive and behavioural factors – particularly gravidity and smoking – were associated with up to 2 years later menopause. With regard to the relevance of age at menarche and menopause on adult CVD risk factors, blood pressure and anthropometry showed highly significant, albeit weak, inverse associations with age at menarche that were approximately four times as strong as their positive associations with age at menopause; although the associations of blood pressure with each reproductive factor were attenuated by at least half with adjustment for current BMI. The small effects of age at menarche and menopause on these known CVD risk factors indicate that differences in either reproductive factor are unlikely to impact on CVD rates in China to the same extent as known risk factors such as smoking. However, there may be effects of age at menarche and menopause on blood-based CVD risk factors, such as cholesterol and its fractions which could not be assessed in this study. Notably, the trends and associations seen in this study showed large variations by area and SES.

Although restricted to cross-sectional analyses (with the usual related problems of possible confounding and inability to establish causality), this thesis contributes new information on the correlates of age at menarche and menopause among Chinese women born in the mid-20th century, and provides a starting point for further prospective work on the controversy surrounding the association of reproductive history with CVD.

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Chapter 13. Appendices

Appendix A:

Overview of literature on oestrogen exposure and cardiovascular disease

The literature on the association between oestrogen and CVD can be broadly subdivided into the following exposure categories: HRT use, OC use and endogenous oestrogen. With regards to exogenous oestrogen exposure (HRT and OC use), both observational studies as well as randomised controlled trials (RCTs) have examined the effect of these exposures on various cardiovascular outcomes including myocardial infarction (MI) and stroke. Endogenous oestrogen has been investigated through observational studies examining primarily the association between age at menopause and CVD, using age at menopause as a measure of lifetime endogenous oestrogen exposure (EOE). In a few instances, a derived measure of lifetime EOE incorporating other elements of reproductive history has been used [1, 2] but one study shows that age at menopause has equivalent predictive value for CVD [3]. This overview contains a concise summary of the association between these major groups of oestrogen exposure and CVD.

Exogenous oestrogen exposure versus CVD

OCs are distinguished from HRT by the type of oestrogen and progestogens found in each - with OCs using synthetic alkylated oestrogens in contrast to the natural oestrogens of HRT - as well as the different effects of each on metabolic and haemostatic parameters [4]. The largest body of work relates to HRT and is the source of controversy surrounding the hypothesis that greater exposure to oestrogen confers cardioprotection.

While results from several large observational studies indicated that HRT may protect against MI and stroke [5-14] and a meta-analysis of studies until 1991 by Stampfer and Colditz showed a relative risk of 0.58 (95% CI 0.48-0.69) among HRT users in cohort studies with internal controls [15], RCTs failed to show any effect [16-23]. A Cochrane review on use of HRT for prevention of CVD undertook a meta-analysis of the major RCTs of the last 2 decades [24]. Results did not show any protection of HRT against CVD deaths or non-fatal MI or stroke. The primary prevention data (drawn predominantly from the Women's Health Initiative) showed an overall increased hazard of non-fatal MI and stroke with HRT (Figure 1). Secondary prevention data - dominated by the Heart and Estrogen/progestin Replacement Trial - showed no overall effect on hazard of either non-fatal MI or stroke (Figure 2). Both sets of data showed a greater hazard for stroke compared to non-fatal MI implying that HRT affects vascular disease to a different extent depending on site. As a result, the Cochrane review concluded that current evidence did not support the use of HRT for either primary or secondary prevention of CVD in postmenopausal women.

There may be several reasons for the disparity in results between observational studies and RCTs on this topic but the most likely reason is residual confounding in the observational studies. RCTS and observational studies have drawn from populations with different underlying characteristics. Women who choose to take HRT (as opposed to being randomised to it in the course of a trial) generally have higher socioeconomic status [25], better risk profiles [26] as well as better compliance adding to a healthy cohort effect [27]. HRT has different effects on CVD depending on age at initiation and years since menopause [23] with earlier use together with longer duration showing greater benefit. The Women's Health Initiative (WHI) is the largest study to date on the use of HRT in primary prevention of CVD and constituted the vast majority of Cochrane data for the primary prevention analyses. This study used both an observational study of over 53 000 women and a RCT of over 16 000 women to examine the effect of HRT on CVD [28] and so is an excellent opportunity to compare results between women drawn from the same population through the same 40 WHI clinical centres. The initial sets of results from the different arms were consistent with other studies of the same design but there was a 39-48% lower hazard ratio after adjustment for age in the observational arm [26]. Prentice et al re-analysed the WHI data accounting for underlying differences in the study populations of the cohort versus RCT arms e.g. differential adherence patterns. Although adjustment for age and traditional confounders by time since HRT initiation raised the level of agreement between the findings of the two study arms to over 80% [26], there was an unaccounted-for residual difference in the CVD hazard ratios of the different arms, particularly for stroke which was statistically significant [29]. This suggests that, while the majority of the discrepancy can be explained by classic confounding, the difference in CVD hazard ratios, especially in the case of stroke, is partly due to factors beyond those taken into account even in this re-analysis and requires further investigation.

The only evidence currently available on the relationship between OC use and CVD comes from observational studies. A meta-analysis by Baillargeon et al (2005) reviewed evidence from 1980-2005 on the association between current use of low-dose OCs (the type most commonly in use at present) and CVD and found increased odds ratios (ORs) for both MI and ischaemic stroke [30]. There was a greater hazard for stroke compared to MI (Figure 3) which is consistent with the findings of the Cochrane Collaboration on the effect of HRT on stroke and non-fatal MI (Figures 1-2).

This meta-analysis only included case-control studies as all cohort studies considered were excluded for failing to observe more than 10 cases of CVD events due to insufficient numbers of women on low-dose OCs. Studies conducted in the United States yielded lower summary ORs for both outcomes than studies conducted in Europe. Population-based controls also yielded lower summary ORs compared to hospital-based controls. Both are examples of the kind of sampling bias to which case-control studies are prone. Population-based controls are considered more desirable as they are more representative of the general population than hospital-based controls [31]. More stringent screening for risk factors prior to prescription of OC in the US may result in a higher proportion of women with better risk profiles, which would account for the difference between findings in European versus American studies [32]. However, the results from several other meta-analyses support the finding that current OC use increases the risk of CVD [33, 34] particularly in those women who already have risk factors for CVD [35, 36].

Endogenous oestrogen exposure versus CVD

The relationship between endogenous oestrogen exposure (EOE) and CVD can only be investigated through observational studies. A meta-analysis by Atsma et al of studies using age of menopause as the exposure included 12 studies from 1966-2004 and found a pooled relative risk of 1.25 (95% CI 1.15-1.35) per year later menopause, which became 1.38 (95%CI 1.21-1.58) when adjusted for current age and smoking [37]. In sub-group analyses for age at menopause, women who had a bilateral oophorectomy had a relative risk of 4.55 (95% CI, 2.56-8.01) compared to women with natural menopause who had a relative risk of 1.27 (95% CI, 1.14-1.43). Adjustment for age and smoking reduced the difference in relative risk between pre- and postmenopausal women of 1.36 (95% CI, 1.15-1.60) to 0.96 (95% CI, 0.77-1.21). In general, these studies were large, recent, prospective studies. However, there was significant heterogeneity between the studies as well as an indication of publication bias, so the included studies may not represent the full extent of work on this association. There may also be residual confounding as studies categorised smoking and age differently and the meta-analysis combined non-fatal CVD events with mortality to obtain the overall risk estimate. In support of the overall findings, a re-examination of data from one of the studies included showed a 2% reduction in age-adjusted CVD mortality for each year later menopause [38]. In addition, two prospective studies conducted in Asian populations show a similar protective effect of later menopause on (fatal and non-fatal) CVD [2, 39].

A few studies have tried to examine the association between total EOE and CVD via derived measures. There is no convention for calculating lifetime EOE and so various methods have been used. In most cases, this has been done by comparing the duration between menarche and menopause against CVD [1, 2, 40, 41]. However, elements of reproductive history apart from age at menopause - such as gravidity and parity – also show an association with CVD risk in postmenopausal women [42]. Attempts have been made to incorporate other reproductive events where endogenous oestrogen levels fluctuate significantly in relation to other sex hormones in order to calculate the duration of unopposed oestrogen exposure in a woman's reproductive lifetime [3, 43, 44]. In two cases, the derived measure assigned periods of change in unopposed oestrogen for each reproductive event (e.g. 4-9 months per pregnancy) and assumed that the change in level of oestrogen was constant for this period [3, 43]. The total oestrogen exposure period was calculated as duration between age at menarche and menopause and then each period of change was deducted from the total exposure period to calculate a final duration of unopposed oestrogen exposure. Merz et al attempted to account for higher oestrogen levels during OC use and pregnancy by also calculating a "supra-total estrogen time" through the addition of all periods of increased oestrogen exposure to the duration between menarche and menopause [44].

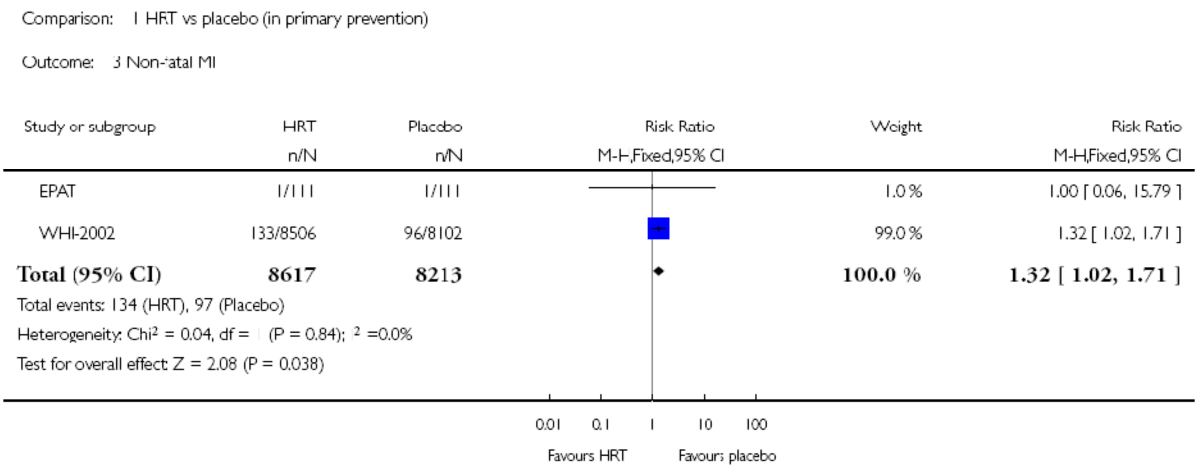
Examination of lifetime EOE (via these various derived measures) with CVD events has produced inconsistent results [2, 3, 40, 41, 43, 44]. Although 3 studies did not find an association between lifetime EOE and CVD [2, 43, 44], one study found a protective but non-significant effect of longer lifetime EOE [40] and two other studies found a significant protective effect of longer lifetime EOE for CVD [3, 41]. Another study comparing lifetime EOE with CVD risk factors found significant inverse associations for cholesterol levels and positive associations for anthropometry [1]. In these studies, different populations, different methods for deriving exposure categories and different outcomes measured prevent aggregation or direct comparison of results. Consequently, there is currently no good evidence on the association between lifetime EOE and CVD.

Direct comparisons of age at menopause and derived measures of lifetime EOE did not find any difference in predictive value for CVD mortality between age at menopause and a derived measure of lifetime EOE [3, 40, 43]. Atsma et al did not find any additional predictive value of either age at menopause or a derived measure of lifetime EOE beyond a model using age, systolic blood pressure, total to HDL cholesterol ratio, current smoking, glucose level, and body mass index $\geq$ 30 kg/m^2 as predictors for ankle-arm index as a proxy for cardiovascular morbidity and mortality [43]. While an approach that takes into account multiple reproductive variables is more sophisticated, the method is based on a series of assumptions. There is no assessment of how closely the final measure approximates the actual changes in unopposed oestrogen throughout the reproductive years. Such an assessment is unlikely to occur given the difficulty in directly measuring oestrogen levels over time. Although a derived measure may not always confer additional predictive value to age at menopause for CVD mortality [3, 40, 43], an approach that adjusts for all significant reproductive events is more likely to give an accurate picture of lifetime unopposed EOE than simply using the duration between menarche and menopause [42]. Alternatively, examining the relationship between individual reproductive variables related to changing levels of endogenous oestrogen and CVD may provide more information than a simplistic composite measure of endogenous oestrogen exposure.

Conclusion

There remains controversy over the association between oestrogen exposure and CVD. Results from studies on exogenous oestrogen exposure are contradictory, with the protective effect seen in observational studies not reproduced in the RCTS. Most of this discrepancy may be due to classical confounding based on study design and populations, but further research is needed to clarify how exogenous oestrogen exposure may affect CVD and how this effect may vary with age, type of oestrogen and duration of exposure. Observational studies on the association of endogenous oestrogen exposure to CVD suggest a protective effect. The largest body of evidence on the association between endogenous oestrogen exposure and postmenopausal CVD uses age at menopause as the exposure, which does not reflect the impact of other significant reproductive events. Overall, limited research has been done on the effect of other reproductive variables associated with changing levels of endogenous oestrogen on CVD. There is evidence of a protective effect of later menopause and longer lifetime endogenous oestrogen exposure on CVD but attempts at formulating a comprehensive measure incorporating all significant events in reproductive history have not been successful in accurately reflecting lifetime endogenous oestrogen. Development of a more valid composite measure may be facilitated by closer examination of the individual associations between these reproductive variables and CVD which in turn provide a clearer picture of the overall association between endogenous oestrogen and CVD.

Figure 1: Summary risk ratios for HRT versus placebo in primary prevention of non-fatal MI and stroke - Cochrane review on HRT for preventing cardiovascular disease in post-menopausal women [24]



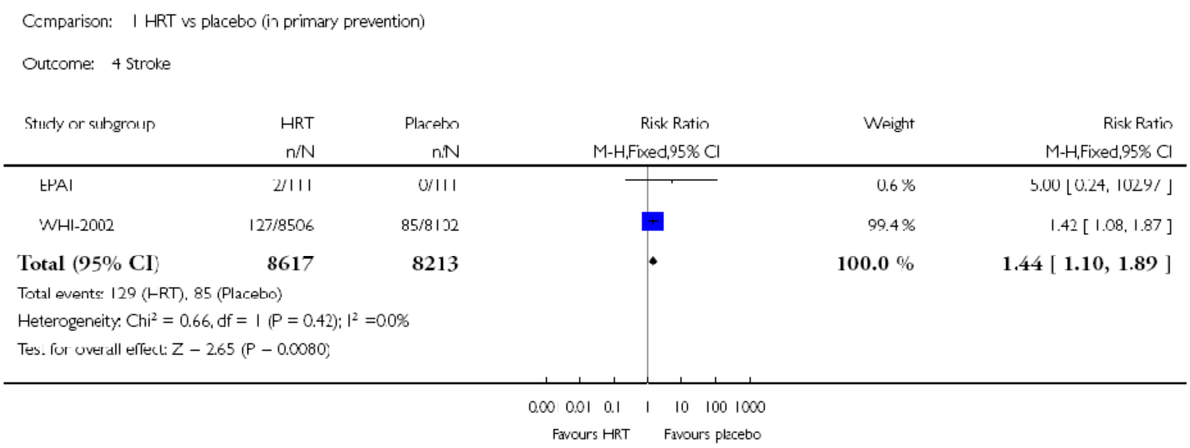


Figure 2: Summary risk ratios for HRT versus placebo in secondary prevention of non-fatal MI and stroke - Cochrane review on HRT for preventing cardiovascular disease in post-menopausal women [24]

Comparison: 2 HRT vs placebo (secondary prevention only)

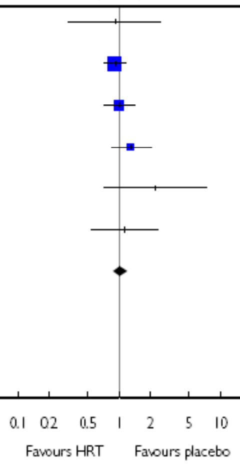
Outcome: 3 Non-fatal MI

Study or subgroup	HRT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ERA	6/100	7/105		2.8 %	0.90 [0.31, 2.59]
HERS	116/1380	129/1383		52.6 %	0.90 [0.71, 1.14]
HERS II	61/1156	62/1165		25.2 %	0.99 [0.70, 1.40]
SPRIT 2002	41/513	31/504		12.8 %	1.30 [0.83, 2.04]
WAVE	9/210	4/213		1.6 %	2.28 [0.71, 7.30]
WEST	14/337	12/327		5.0 %	1.13 [0.53, 2.41]
Total (95% CI)	**3696**	**3697**		**100.0 %**	**1.01 [0.85, 1.20]**

Total events: 247 (HRT), 245 (Placebo)

Heterogeneity: $Chi^2 = 4.11$, df = 5 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 0.10 (P = 0.92)



Comparison: 2 HRT vs placebo (secondary prevention only)

Outcome: 4 Stroke

Study or subgroup	HRT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
ERA	5/100	6/105		2.5 %	0.88 [0.28, 2.78]
HALL	2/40	0/20		0.3 %	2.56 [0.13, 50.95]
HERS	106/1380	96/1383		40.8 %	1.11 [0.85, 1.44]
HERS II	59/1156	55/1165		23.3 %	1.08 [0.76, 1.55]
SPRIT 2002	10/513	6/504		2.6 %	1.64 [0.60, 4.47]
WAVE	26/210	15/213		6.3 %	1.76 [0.96, 3.22]
WEST	63/337	56/327		24.2 %	1.09 [0.79, 1.51]
Total (95% CI)	**3736**	**3717**		**100.0 %**	**1.15 [0.97, 1.36]**

Total events: 271 (HRT), 234 (Placebo)

Heterogeneity: $Chi^2 = 3.14$, df = 6 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 1.65 (P = 0.10)

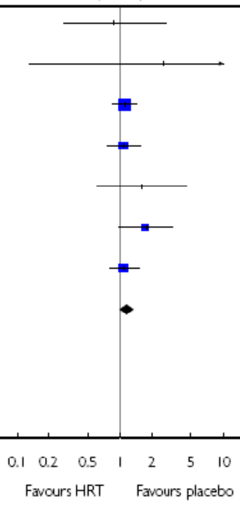
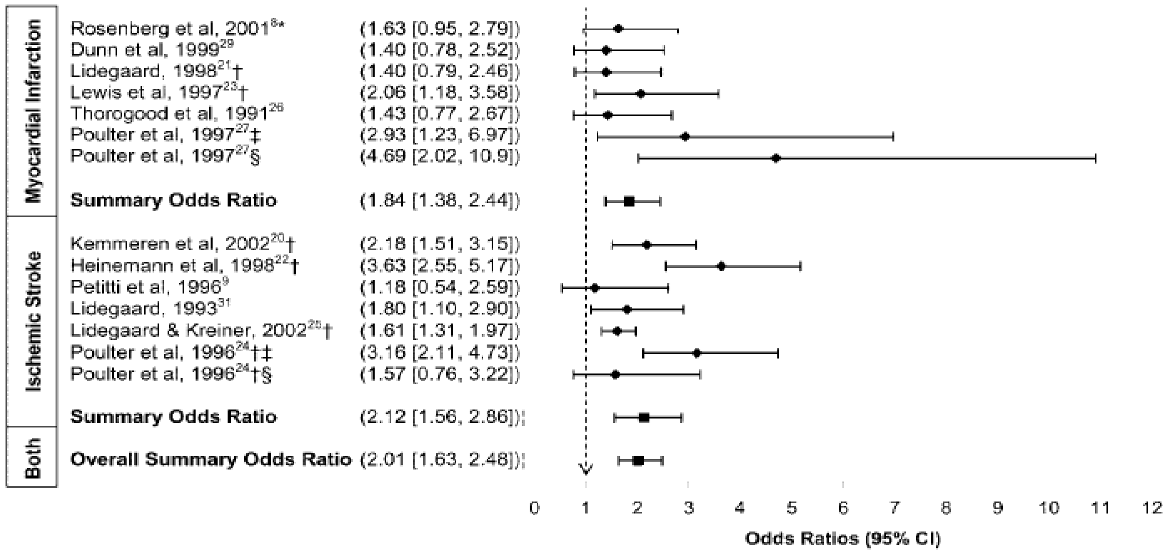
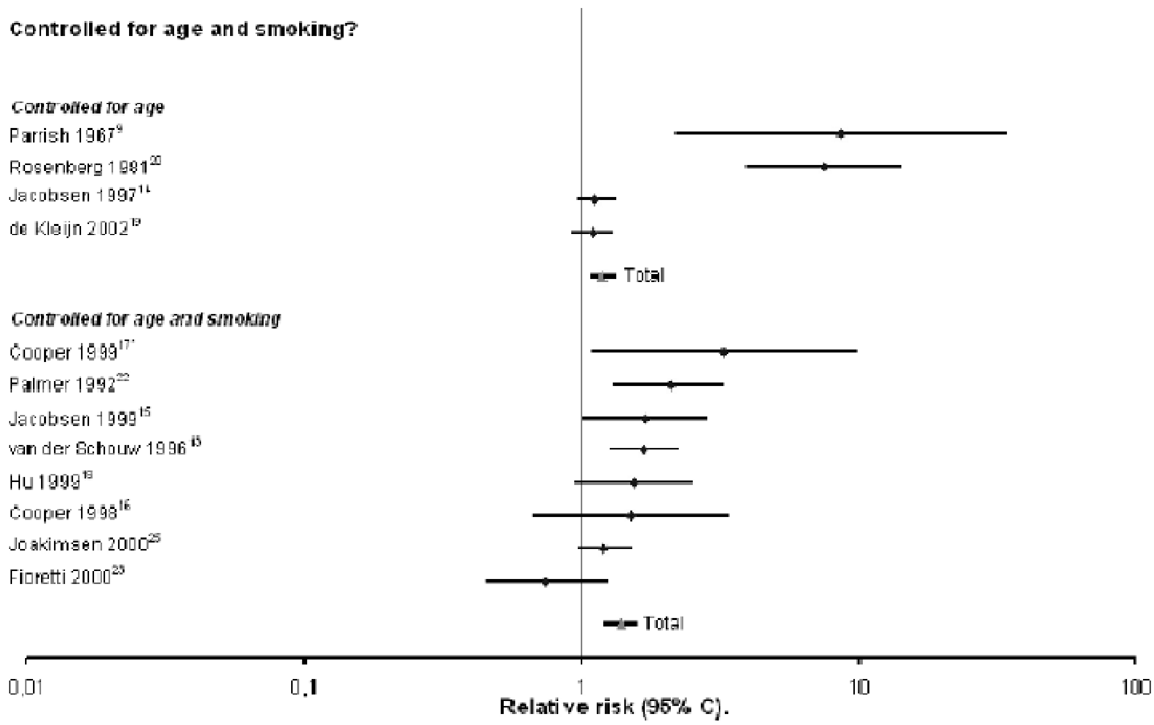


Figure 3: Summary odds ratios for case-control studies included in meta-analysis conducted by Baillargeon et al on association between current low-dose OC use and CVD [30]



Meta-analysis of the estimated risk for cardiovascular outcome related to the current use of low-dose OCs. Values are the OR and 95% CI. Comparisons are for current *vs.* noncurrent use, except for *, which is current *vs.* never use. †, In these studies, the ORs were presented separately for second- and third-generation OCs, and they were combined using fixed-effect method to determine the ORs for all low-dose OCs. ‡, Results reported for developing countries only. §, Results reported for European countries only. ¦, Significant heterogeneity in the study results using a general variance-based method.

Figure 4: Early menopause and CVD risk, stratification by controlling for age and smoking, with menopause age category including 50 years as the reference [37]



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Appendix B:

Original full China Kadoorie Biobank (formerly known as the Kadoorie Study of Chronic Disease in China) baseline survey questionnaire

June 10, 2004

Kadoorie Study of Chronic Disease in China

【Questionnaire】

Clinical Trial Service Unit & Epidemiological Studies Unit,
Nuffield Department of Clinical Medicine, University of Oxford, UK
&
Chinese Centre for Disease Control and Prevention, Beijing, P. R. China

Section 1: Background information

1.1 Study ID: ☐☐☐☐☐☐☐☐☐☐ *(The date & time of interview will be recorded by computer)*

1.2 Name____________, **Sex** : Male ☐ Female ☐ , **Name of spouse**________________

1.3 Date of birth: ☐☐☐☐ Year ☐☐ Month ☐☐ Day

1.4 National ID number (if no, put #) ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

1.5 Home address : _____ Province _____ City_________ District/County _____ Street/Village

Home telephone: Not available ☐ , Yes: ☐☐☐☐–☐☐☐☐☐☐☐☐☐☐☐

1.6 What is the highest level of school education you ever received?

- ☐ No formal school
- ☐ Primary School
- ☐ Middle School
- ☐ High School
- ☐ Technical school / college
- ☐ University

1.7 What is your current occupation?

- ☐ Agriculture & related workers
- ☐ Factory worker
- ☐ Administrator / manager
- ☐ Professional / technical
- ☐ Sales & service workers
- ☐ Retired
- ☐ House wife / husband
- ☐ Self-employed
- ☐ Unemployed
- ☐ Other or not stated

1.8 How many people living together in the household? ☐☐ persons

1.9 What is your current marital status?

- ☐ Married
- ☐ Widowed
- ☐ Separated / divorced
- ☐ Never married

1.10 What is the total income last year in your household?

- ☐ <2,500 yuan
- ☐ 2,500-4,999 yuan
- ☐ 5,000-9,999 yuan
- ☐ 10,000-19,999 yuan
- ☐ 20,000-34,999 yuan
- ☐ ≥35,000 yuan

1.11 Do you have any health care cover and following items in your household?

Yes	No	
☐	☐	Health care cover
☐	☐	Own house / apartment
☐	☐	Toilet for private use
☐	☐	Telephone or mobile phone
☐	☐	Motor vehicle (e.g. car or motorbike)
☐	☐	Holiday during last five years

Section 2: Tea drinking

2.1 During the past 12 months, how often did you drink any tea?

- ☐ Never or almost never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → ***Go to Q2.3*** (were2.2)

2.2(were 2.1a) **In the past, did you ever have a period of at least 1 year during which you usually drank tea at least once a week?**

- ☐ Yes, → (were 2.1b) if so, how long ago did it end? [ ][ ] Years } ***Go to section 3***
- ☐ No

2.3(were 2.2) **During the past 12 months, on how many days did you drink tea in a typical week?**

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

2.4(were2.3)**At about what age did you start drinking tea in most weeks?** ········· [ ][ ] Years

---

2.5(were2.4)**On days when you drink tea, how many cups do you usually drink?** (choose one only)

Green /Jasmine tea ·········	[ ][ ]	cups/day
Oolong tea ·········	[ ][ ]	cups/day
Black tea ·········	[ ][ ]	cups/day
Other tea ·········	[ ][ ]	cups/day

2.6(were2.5) **How often do you change tea leaves during a day?** ············ [ ][ ] times

---

2.7(were2.6) **About how much tea leaves do you usually add each time?** [ ][ ] Grams

---

2.8(were2.7) **What strength of tea do you usually prefer to drink?**

- ☐ Weak
- ☐ Moderate
- ☐ Strong

2.9(were2.8) **At about what temperature do you usually drink your tea?**

- ☐ Room temperature / warm
- ☐ Hot
- ☐ Burning hot

2.10(were2.9)**Has your tea consumption changed significantly compared with that some years ago?** ☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

---

Section 3: Alcohol consumption

3.1(were3.0) **Have you drunk any alcohol today?** ☐ Yes , ☐ No

3.2(were3.1)**During the past 12 months, how often did you drink any alcohol?**

- ☐ Never or almost never
- ☐ Only occasionally
- ☐ Only at certain seasons
- ☐ Every month but less than weekly
- ☐ Usually at least once a week → ***Go to Q3.4*** (wereQ3.2)

3.3(were3.1a)**In the past, did you ever have a period of at least 1 year, during which you usually drank some alcohol at least once a week?**

- ☐ Yes, →(were 3.1b) If so, how long ago did it e[ ][ ] Years
- ☐ No

} ***Go to section 4***

3.4(were3.2)**During the past 12 months, on how many days did you drink alcohol in a typical week?**

- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

3.5(were3.3)**At about what age did you start drinking some alcohol in most weeks?** [ ][ ] Years

---

3.6(were3.4) **On days when you drink, how much alcohol do you usually drink in a day?**
(Can choose up to 3 types of alcohol for special occasions; for beer, 1 large bottle=2 small ones)

Alcohol type	On a typical day (choose one)		On a special day when you drink a lot		Last time when you drank	
Beer (large)	[ ][ ]	Bottle	[ ][ ]	Bottle	[ ][ ]	Bottle
Rice Wine	[ ][ ]	liang	[ ][ ]	liang	[ ][ ]	liang
Wine	[ ][ ]	liang	[ ][ ]	liang	[ ][ ]	liang
Spirit (≥50% alcohol)	[ ][ ]	liang	[ ][ ]	liang	[ ][ ]	liang
Spirit (<50% alcohol)	[ ][ ]	liang	[ ][ ]	liang	[ ][ ]	liang

3.7(were3.5)**On a typical day when you drink alcohol, when do you usually take the drink?**

- ☐ Usually drink with the meal
- ☐ Usually drink between or after the meals
- ☐ No regular pattern

3.8(were3.6)**After drinking alcohol, do you usually experience hot flushes or dizziness?**

- ☐ Yes, soon after first mouthful
- ☐ Yes, after drinking small amount of alcohol
- ☐ Yes, but only after drinking large amount of alcohol
- ☐ No

3.9(were3.7)**During the past month, how often have you drunk alcohol in the morning?**

- ☐ Never
- ☐ <1 day/week
- ☐ A few days a week
- ☐ Daily or almost daily

3.10(were3.8)**During the past month, have you ever had the following experiences?**

Yes	No	
☐	☐	Unable to work or to do anything because of drinking
☐	☐	Felt depressed, irritated or couldn't control yourself after drinking
☐	☐	Could not keep away from drinking
☐	☐	Had shakes when you stopped drinking

3.11(were3.9) **Has your alcohol consumption changed significantly compared with that some years ago?**

- ☐ About the same as before
- ☐ Has increased a lot
- ☐ Has decreased a lot

Section 4: Smoking history

4.1(were4.0) **Have you smoked any tobacco today?** ☐ **Yes ,** ☐ **No,** → if yes, how many: __ total, __in last hour

4.2(were4.1)**How often do you smoke tobacco now?**

- ☐ Do not smoke now
- ☐ Only occasionally
- ☐ Yes, on most days
- ☐ Yes, daily or almost every day } → ***Go to Q4.7*** (were Q4.5)

4.3(were4.2)**In the past, how frequently did you smoke?**

- ☐ Did not smoke
- ☐ Smoked only occasionally
- ☐ Smoked on most days
- ☐ Smoked daily or almost every day } → ***Go to Q 4.5*** (were Q4.3)

4.4(were4.2a)**In your life time, have you smoked a total of at least 100 cigarettes or equivalent?**

- ☐ Yes
- ☐ No } → ***Please go to section 5***

4.5(were4.3)**How many years ago did you last stop smoking regularly?** ☐☐ Years

4.6(were4.4)**What was your main reason for stopping?**

- ☐ Physical illness that you already had
- ☐ Money
- ☐ Health concerns (about future illness)
- ☐ Family against
- ☐ Other

4.7(were4.5)**At about what age did you first start smoking on most days?** ☐☐ Years

4.8(were4.6)**What tobacco did you use when you first started smoking on most days?**

Mainly cigarette ☐, Mainly non-cigarette ☐, Mixed types ☐

↳ (4.6a) If so, have you always smoked some cigarettes on most days, never having a month or more without them? Yes ☐, No ☐

4.9(were4.7)**How much tobacco do you usually smoke (or did you smoke before giving up)?**

Filter cigarettes (factory)	☐☐	number/day
Non-filter cigarettes (factory)	☐☐	number/day
Hand-rolled cigarettes	☐☐	liang/month
Pipe or water pipe	☐☐	liang/month
Cigars	☐☐	number/day

4.10(were4.9) **How deeply do you usually inhale the smoke?**

- ☐ Mouth only
- ☐ Throat
- ☐ Lung → 4.9a Have you always inhaled the smoke into your lung when smoking? Yes ☐, No ☐

4.11(were4.10)**Has your tobacco consumption changed significantly compared with that some years ago?**

☐ About the same as before, ☐ Has increased a lot, ☐ Has decreased a lot

---

Section 5: Diet

5.1(were5.2)**During the past 12 months, about how often did you eat the following foods?**

	Daily	4-6 days per week	1-3 days per week	Monthly	Never/rarely
Rice	☐	☐	☐	☐	☐
Wheat	☐	☐	☐	☐	☐
Other staple food (corn, millet etc.)	☐	☐	☐	☐	☐
Meat	☐	☐	☐	☐	☐
Poultry	☐	☐	☐	☐	☐
Fish/sea food	☐	☐	☐	☐	☐
Fresh eggs	☐	☐	☐	☐	☐
Fresh vegetables	☐	☐	☐	☐	☐
Soybean products	☐	☐	☐	☐	☐
Preserved vegetables	☐	☐	☐	☐	☐
Fresh fruit	☐	☐	☐	☐	☐
Dairy products (milk, yogurt)	☐	☐	☐	☐	☐

5.2(were5.3)**During the past 12 months, have you taken the following supplements regularly?**

Yes	No	
☐	☐	Fish oil/cod liver oil
☐	☐	Vitamins
☐	☐	Calcium/iron/zinc
☐	☐	Ginshen (at least 5 or more times during a year)
☐	☐	Other herbal products

5.3(were5.3a)**Have you ever experienced any severe food shortage?** ☐Yes, ☐ No → ***Go to Q5.6(wereQ5.3c)***

5.4(were5.3a1)**What year was the worst food shortage you experienced?** ____________ **years**

5.5(were5.3b)**During the most severe food shortage you experienced:**

5.5.1− did you lose weight? ☐ Yes, ☐ No, → If yes, about how much? _____ *jin,*

5.5.2− did you develop any specific disease related to food shortage? ☐ Yes, ☐ No

5.6(were5.3c)**How many years have you had a refrigerator in your home?** ☐☐ Years

5.7(were5.4) **During the past month, about how often did you eat hot spicy food?**

☐ Never or almost never
☐ Only occasionally
} → ***Go to section 6***
☐ 1-2 days/week
☐ 3-5 days/week
☐ Daily or almost every day

5.8(were5.5)**At what age did you start to eat spicy food at least once a week?** ☐☐ Years

5.9(were5.6)**What strength of spicy food do you usually prefer to eat?**

☐ Weak, ☐ Moderate, ☐ Strong

5.10(were5.7)**On day when you eat spicy food, what are the main sources of spice usually used?**

Yes	No	
☐	☐	Chili sauce
☐	☐	Chili oil
☐	☐	Dried chili pepper
☐	☐	Fresh chili pepper
☐	☐	Other or don't know

Section 6: Passive smoking & indoor air pollution

6.1 Have you ever lived with smoker in the same house for at least 6 months?

- ☐ Never
- ☐ Yes, but not now
- ☐ Yes, at present } → ***If yes, duration of living together*** [|] years

---

6.2 How frequently are you exposed to other people's tobacco smoke either at home, workplace or in public places? *(i.e. a minimum of 5 consecutive minutes each time)*

- ☐ Never or almost never
- ☐ Occasionally (<1 time/week) } → ***Go to Q6.4***
- ☐ 1-2 days/week
- ☐ 3-5 days/week
- ☐ Daily or almost every day

6.3 What is the usual duration of your exposure per week? [|] Hours

---

6.4 During past year, how long did you store pesticides at home? [|] Months

---

6.5(were6.4a)**Please tell us the duration you lived in 3 most recent houses** (each for at least 1 year)?

Present house [|] years

Previous house [|] years

The house before previous [|] years

6.6(were6.5) **In your present & two previous houses, how often did you cook at home?**

- ☐ Daily
- ☐ Weekly
- ☐ Monthly
- ☐ Never/Rarely → ***Go to Q6.10*** **(wereQ6.8)**
- ☐ No cooking facility → ***Go to Q6.11*** (wereQ6.11)

6.7(were6.6)**In your present & two previous houses, what was the main cooking fuel used?**

- ☐ Gas
- ☐ Coal
- ☐ Wood
- ☐ Eletricity
- ☐ Other

6.8(were6.7)**In your present & two previous houses, what was the main cooking oil used?**

- ☐ Rapeseed
- ☐ Peanut
- ☐ Soybean
- ☐ Lard
- ☐ Other

6.9(were6.7a)**How much time have you spent on cooking so far today?** [|] minutes

---

6.10(were6.8)**In your present & two previous houses, did your stove(s) all have a chimney / extractor?**

☐ Yes ☐ Not all stoves ☐ No

6.11(were6.9)**In your present & two previous houses, was your stove always kept under slow burning throughout the day?**

☐ Yes, always ☐ Yes, sometimes ☐ No → if ticked, ***Go to Q6.14***

6.12(were 6.9a) **If yes , types of the fuel most commonly used?**

☐ Smokeless coal ☐ Coal brick / Coalite

☐ Smoky coal ☐ Other

6.13(were 6.9b) **And , the place where stove was usually kept?**

☐ Inside the house ☐ Outside the house

6.14(were6.11)**In winter, did you normally heat your house?**

☐ Yes, ☐ No

6.15 If yes, what was the main heating fuel used?

☐ Central heating ☐ Wood

☐ Gas ☐ Electricity

☐ Coal ☐ Other

6.16(were6.12)**From what year did the inside of your house tend to be coal-smoky in winter?**

☐ Never → if ticked, ***Go to section7***

☐ Ever since childhood

☐ Since the year: _________ year

6.17(were6.13)**In what year did the inside of your house stop being really coal-smoky in winter?**

☐ In the year: _________ year

☐ Still is

Section 7: Personal & family medical history

7.1 How is your current general health status?

7.1.1 Self-rated health status?
- ☐ Excellent
- ☐ Good
- ☐ Fair
- ☐ Poor

7.1.2. Compared to someone of your own age?
- ☐ Better
- ☐ About the same
- ☐ Worse
- ☐ Don't know

7.2 If you were walking on level ground with other healthy people of the same age, would you usually:

7.2.1 Become short of breath?
- ☐ Yes
- ☐ No
- ☐ Disabled

7.2.2 Slow down due to chest discomfort?
- ☐ Yes
- ☐ No
- ☐ Disabled

7.3 During the past 12 months, have you usually had the following symptoms?

7.3.1 Cough frequently?
- ☐ No
- ☐ Yes, for <3 months
- ☐ Yes, for ≥3months

7.3.2 Cough up sputum after getting up in the morning?
- ☐☐ No
- ☐☐ Yes, for <3 months
- ☐☐ Yes, for ≥3 months

7.4 Has a doctor EVER told you that you had had the following disease?

	Diagnosed disease? Yes	Diagnosed disease? No	Age at first diagnosis	Still on treatment? Yes	Still on treatment? No
Diabetes	☐	☐	______	☐	☐
CHD	☐	☐	______	☐	☐
Stroke or TIA	☐	☐	______	☐	☐
Hypertension	☐	☐	______	☐	☐
Rheumatic heart dis.	☐	☐	______	☐	☐
TB	☐	☐	______	☐	☐
Emphysema/bronchitis	☐	☐	______	☐	☐
Asthma	☐	☐	______	☐	☐
Cirrhosis/chronic hepatitis	☐	☐	______	☐	☐
Peptic ulcer	☐	☐	______	☐	☐
Gallstone/gallbladder dis.	☐	☐	______	☐	☐
Kidney disease	☐	☐	______	☐	☐
Fracture	☐	☐	______	☐	☐
Rheumatoid arthritis	☐	☐	______	☐	☐
Psychiatric disorders	☐	☐	______	☐	☐
Neurasthenia	☐	☐	______	☐	☐
Head injury	☐	☐	______	☐	☐
Cancer*	☐	☐	______	☐	☐

For CHD, stroke, and hypertension what is the current medication:

1. Aspirin
2. ACE-I
3. Beta-blocker
4. Statins
5. Diuretics
6. Ca^{++} antagonist

& for diabetes, the above list plus

7. Chlorpropamide or metformin
8. Insulin

***If yes, please indicate the site of cancer** ☐ *(If more than one, choose the one that occurred first)*

0. Lung 1. Esophagus 2. Stomach 3. Liver 4. Intestine 5. Breast 6. Prostate 7. Cervix 8. Other

7.5 **Have many blood transfusions have you ever received?** *(If none, put 0)* ☐☐ times

7.6(were7.5a)**How many times have you ever donated blood for financial payment?**

(If none, put 0) ☐☐ times

7.7(were7.6)**About how often do you have bowel movements each week?**

- ☐ More than once on most days
- ☐ About daily
- ☐ Once every 2-3 days
- ☐ Less than 3 times a week

7.8(were7.7)**How often do your gums bleed when you brush your teeth?**

- ☐ Occasionally, rarely or never
- ☐ Sometimes
- ☐ Always
- ☐ Brush teeth rarely or never

7.9(were7.8)**How many brothers & sisters do you have?***(Including half siblings. If unknown, put#)* ☐☐

7.10(were7.9)**How many children do you have?** *(Including only biological ones)* ☐☐

7.11(were7.9a)**Is your mother still alive?**

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.12(were7.9b)**Is your father still alive?**

- ☐ Yes → If ticked, current age: ☐☐
- ☐ No → If ticked, age at death: ☐☐
- ☐ Unknown

7.13(were7.10) **Did any of your parents, siblings or children have following diseases?** *(For sibling and children, please record the number with disease)*

	Stroke	Heart attack	Diabetes	Mental disorder	Cancer
Mother *(tick box)*	☐	☐	☐	☐	☐
Father *(tick box)*	☐	☐	☐	☐	☐
Siblings *(inclu. half)*	☐	☐	☐	☐	☐
Children	☐	☐	☐	☐	☐

Section 8U: Physical activities (Urban)

8.1 During the past 12 months, how active were you at work?

☐ Mainly sedentary (e.g. office worker)
☐ Standing occupation (e.g. guard, shop assistant)
☐ Manual work (e.g. plumber, carpenter)
☐ Heavy manual work (e.g. miner, construction worker)
☐ Retired or housewife/husband or unemployed or disabled → ***If ticked, please go to Q8.8***

8.2(were8.1a) **In a typical week, about how many hours did you usually work? _______ hours**

8.3(were8.2) **During the past 12 months, how did you usually get to work?**

☐ Mainly walk
☐ By motorbike
☐ By bicycle
☐ By bus/car/ferry/train
☐ Mainly stay at home or work near home
↳***If ticked, please go to Q8.8***

8.4(were8.3) **How much time did you spend each day on journey to & from work? _____minutes**

Section 8F: Physical activities (New section for rural farmers)

8.1 During the past 12 months, did your farming work change seasonally?

☐ No → ***go to Q8.3***
☐ Yes

8.2 During the farming season in the last 12 months:

8.2.1 How many months did it usually last? ☐☐ month

8.2.2 What types of work did it usually involve?

☐ manual ☐ Semi-mechanized ☐ Fully mechanized

8.2.3 How many hours did you usually work each day? ☐☐ hours

8.2.4 Of which , how many hours did you sweat or have a much faster heartbeat? ☐☐ hours

---

8.3 In a typical week, how many hours did you usually work in the field? ☐☐ hours

---

8.4 Apart from agriculture work, did you have any other job?

☐ No → ***go to Q8.7***
☐ Yes

8.5 How active were you at work with other job?

☐ Mainly sedentary
☐ Mainly standing
☐ Mainly general manual work
☐ Mainly heavy manual work

8.6 In a typical week, about how many hours did you work at other job? ☐☐ hours

---

8.7 In a typical day how much time did you usually spend on the journey to and from work on foot or by bicycle? ☐☐☐ minutes

---

Section 8C: Physical activities (Common to both rural farmers and urban)

8.8 During the past 12 months, how often did you do exercise in your leisure time?

- ☐ Never or almost never
- ☐ 1-3 times/month

} → ***If ticked, please go to Q8.11***

- ☐ 1-2 times/week
- ☐ 3-5 times/week
- ☐ Daily or almost every day

8.9 What is your main type of exercise? *(tick one box only)*

- ☐ Taichi / Qigong
- ☐ Walking
- ☐ Jogging/aerobic exercise
- ☐ Swimming
- ☐ Ball games (basketball, table tennis, etc)
- ☐ Other (eg. mountain climbing)

8.10 About how many hours per week did you do such exercise in leisure time? ___ hours

---

8.11 In a typical week during the past 12 months, how often did you sweat or have a much faster heartbeat because of heavy physical activities/exercise?

- ☐ Never or almost never
- ☐ <1 time / week

} → ***If ticked, please go to Q8.13***

- ☐ 1-2 times/week
- ☐ 3-5 times/week
- ☐ Daily or almost every day

8.12 About how many hours per week did you do such activities? _______ hours

---

8.13 About how many hours per week did you do house work? _______ hours

8.14 About how many hours per week did you watch TV or read? _______hours

---

8.15 During the past 12 months, has your weight changed significantly?

☐ About the same as before ☐ Yes, gained ≥2.5 kg ☐ Yes, lost ≥2.5 kg

---

8.16 Have you tried to reduce weight in the past 12 months? No ☐, Yes ☐

8.17 How much did you weigh when you were at age 25? (If unknown put #) [| |] jin

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Section 9: Reproductive history (for women)

9.1 How old were you when you had your first menstrual period? ☐☐ Year

9.2 Have you had your menopause?

- ☐ No
- ☐ Yes, currently
- ☐ Yes, had menopause → If so, age of completion of menopause: ☐☐ Year

9.3 How many times have you ever been pregnant? (if none, put 0. Go to Q9.6) ☐☐ times

— **Of which,**

Live birth ☐☐ times → If none, Go to Q9.5 (wereQ9.6)

Still birth ☐☐ times, Spontaneous abortion ☐☐ times, Induced abortion ☐☐ times

9.4 Age and length of breastfeeding at each live birth (twins=one birth)?

Live Birth	Age at end of pregnancy	Months of breastfeeding
1st	☐☐	☐☐
2nd	☐☐	☐☐
3rd	☐☐	☐☐
4th	☐☐	☐☐
5th	☐☐	☐☐

9.5(were9.6)**Have you ever used oral contraceptive pills?**

- ☐ Never → ***If ticked, please go to Q9.8*** (were Q9.9)
- ☐ Past use → **if ticked,** age when you last stopped the pill: ☐☐ Year
- ☐ Current use

9.6(were9.7)**How old were you when you first used oral contraceptives**? ☐☐ Year

9.7(were9.8)**For how long altogether have you used oral contraceptives?** ☐☐ Year

9.8(were9.9)**Have you had a hysterectomy**?

☐ No , ☐ Yes → If yes, age when you had the operation ☐☐ Year

9.9(were9.10)**Have you had one or both ovaries removed?**

☐ No , ☐ Yes → If yes, age when you had the most recent operation ☐☐ Year

9.10(were9.11) **Have you ever had surgery to remove a breast lump?**

☐ No, ☐ Yes → If yes, age when you most recently had the operation ☐☐ Year

Section 10: Sleeping, mood & mental situation

10.1 In general, how satisfied are you with your life?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Neither satisfied nor dissatisfied
- ☐ Unsatisfied
- ☐ Very unsatisfied

10.2 Over the past two years have you had any of the following major events in your life?

Yes	No		Yes	No	
☐	☐	Marital separation/divorce	☐	☐	Major injury or traffic accident
☐	☐	Loss of job/retirement	☐	☐	Death /major illness of spouse
☐	☐	Business bankrupt	☐	☐	Death/major illness of other close family member
☐	☐	Violence	☐	☐	Major natural disaster (e.g. flood & drought)
☐	☐	Major conflict within family	☐	☐	Loss of income / living on debt

---

10.3 During the past month, did you have any of the following for ≥3 days each week?

Yes	No	
☐	☐	Taking >30 minutes to fall asleep after going to bed or waking up in the middle of the night
☐	☐	Waking up early and not being able to go back to sleep
☐	☐	Needing to take medicine (including herbal or sleeping pills) at least once a week to help sleep
☐	☐	Having difficulty staying alert while at work, eating or meeting people during daytime

---

10.4 Do you usually take a daytime nap? ☐ Yes usually, ☐ Yes ,but only in summer , ☐ No

10.5(were10.4a) **Do you snore during sleep?** ☐ Yes, Frequently, ☐ Yes, Sometimes, ☐ No / Don’t know

10.6(were10.5)**How many hours do you typically sleep per day (incl. naps)?** ☐☐ Hours

---

10.7(were10.6)**During the past 12 months, have you had following situations for 2 or more weeks?**
(If answer yes to any of the questions, complete CIDI-A)

Yes	No	
☐	☐	Feeling much more sad, or depressed than usual
☐	☐	Loss of interest in most things like hobbies or activities that usually give you pleasure
☐	☐	Felt so hopeless that you had no appetite to eat even your favourite food
☐	☐	Feeling worthless and useless, everything went wrong was your fault and life is very difficult that there was no way out

---

10.8(were10.7) **During the past 12 months, have you experienced the following situations?**

Yes	No	
☐	☐	Having a period lasting <u>one month or longer</u> when <u>most of time</u> you felt worried, tense, or anxious and it interfered your life *(if yes, complete CIDI-B)*
☐	☐	Having a pain or discomfort in your body lasting ≥3 months that interfered with your life
☐	☐	Having had a spell or an attack when all of sudden felt frightened, anxious, or very uneasy
☐	☐	Having had inexplicable strong fear in situations such as closed space (cave, elevator, airplane etc), in the crowds or public such that you would avoid such situations

---

Section 11: Physical examination

11.1 **Standing height** (without shoes) .... [| | | .] m

11.2 **Sitting height** .... [| | | .] cm

11.3 **Waist** .... [| | | .] cm

11.4 **Hip** .... [| | | .] cm

11.5 **Weight** (without shoes, but in light clothing) .... [| | | .] Kg

11.6 **BMI** .... [| | .] Kg/m^2

11.7 **Impedance** .... [| |] Ω

Staff code [| |]

11.8 **Fat %** (with one decimal point) .... [| | .]

11.9 **Did you take any drugs to lower blood pressure in the last 2 days?** ☐ Yes ☐ No

11.10 **Blood pressure & heart rate** (to be measured after 5 minutes in the seated position)

	First	Second	
SBP	[| |]	[| |]	mmHg
DBP	[| |]	[| |]	mmHg
Heart rate	[| |]	[| |]	bpm

11.11(were11.10a)**Hours since last ate anything (ignore any drinks)? _______ hours** *Staff code*

11.12(were11.11)**Blood sample collected:** Yes (, . Failed ([| |]

11.13(were11. 12) **Lung function & CO levels:**

	First	Second	
CO	[| |]	[| |]	
%COHB	[| | . | |]	[| | . | |]	%
FEV1	[| . | |]	[| . | |]	Liter
FVC	[| . | |]	[| . | |]	Liter

Staff code [| |]

11.14(were11.13)Assessment of subject's cooperation and the reliability of data collected?

Assessment of subject's cooperation?

☐ Good
☐ Fair
☐ Poor

11.15 Assessment of the reliability of the information collected?

☐ Good
☐ Fair
☐ Poor

Date of interview ______Year______Month____Day, **Signature of interviewer__________**