Life course effects on age at menopause among Bangladeshi sedentees and migrants to the UK

Lorna Murphy[1,3]
Lynnette Sievert[1]
Khurshida Begum[2]
Taniya Sharmeen[2]
Elaine Puleo[3]
Osul Chowdhury[4]
Shanthi Muttukrishna[5]
Gillian R Bentley[6]

[1]Department of Anthropology, UMass Amherst, USA
[2]Department of Anthropology, University College London, UK
[3]School of Public Health, UMass Amherst, USA
[4]M.A.G. Osmani Medical College, Sylhet, Bangladesh
[5]Department of Obstetrics and Gynecology, University College Cork, Ireland
[6]Department of Anthropology, Durham University, UK

Corresponding Author:
Lorna Murphy
Department of Epidemiology and Biostatistics
School of Public Health
410 Arnold House
715 North Pleasant Street
UMass Amherst
Amherst, MA 01003
(413) 387-5966
lmurp0@schoolph.umass.edu

Abbreviated Title: Age at menopause

Funding: NSF Grant #0548393; Wolfson Research Institute, Durham University; Institute of Advanced Study, Durham University; Sigma Xi

Abstract:

Objectives: To assess how different variables experienced across the life course, but particularly during early life, might affect age at menopause among 174 Bangladeshi migrants to London by comparing them to 157 non-migrant sedentees and 154 women of European descent in London.

Methods: Participants were aged 35-59 years, with no exogenous hormone use in the past 3 months, not pregnant or lactating, with no history of hysterectomy or oophorectomy. Face-to-face interviews and anthropometric measures were carried out. In addition to mean recalled age at natural menopause, median age was computed by probit analysis. Ages at menopause were examined by bivariate and Cox regression analyses in relation to demographic, reproductive, and lifestyle variables, and in relation to potential exposure to cyclones in early childhood.

Results: Ages at menopause were significantly earlier among Bangladeshi sedentees and immigrants compared to Londoners of European origin. Ages at menopause were earlier among sedentees compared to immigrants. Urban birthplace, more infectious diseases during childhood, and lower levels of education increased the risk of an earlier menopause.

Conclusions: Changes in environmental conditions during adulthood appeared to modify age at menopause among Bangladeshi immigrants in London compared to women living in Bangladesh; however, Bangladeshi immigrants still experienced an earlier age at menopause compared with their London neighbors of European descent.

Keywords: age at menopause, migration, Bangladeshis, early life, development, life course, cross-cultural comparisons

Introduction:

The purpose of this study is to evaluate the impact of life experience, particularly early life, on age at menopause among middle class, relatively affluent Bangladeshi women who either migrated to London during adulthood (aged >16 years) or remained as sedentees in Sylhet, northeast Bangladesh. These women are compared to a group of white women of European origin who live in London and were raised in the UK. The variables of concern during early life include place of birth (rural vs. urban), exposure to severe cyclones in Bangladesh during the first two years of life, exposure to infectious and parasitic diseases during childhood, childhood nutrition (measured by adult height), and level of education. Variables of concern that affect women later in life include parity, financial status, and tobacco use.

Age at menopause is determined by a combination of initial oocyte numbers and the rate of loss of ovarian follicles across the course of the female lifespan (Broekmans et al. 2009; Bukovsky 2010; Hansen et al. 2008; te Velde et al. 1998) both of which can be influenced by genetic (Stolk et al. 2012), environmental (Sakata et al. 2011), and lifestyle factors (Gold et al. 2001; Morris et al. 2012). As a result, a wide range of variation in age at menopause has been documented across diverse populations (Henderson et al. 2008; Johnston 2001; Reynolds and Obermeyer 2005; Sievert 2006; Thomas et al. 2001). In developed, industrialized countries, the median age of menopause is relatively high at 50 to 52 years (Cramer et al. 1995; Gold et al. 2001; McKinlay et al. 1972; Reynolds and Obermeyer 2003), but in South Asia reported mean and median ages at menopause are often much lower. For example, in India, the average age at menopause has been variously calculated as 48.0 (Kriplani and Banerjee 2005), 46.8 (Kapur et al. 2009), 48.7 (Bairy et al. 2009), and 48.7 (Kakkar et al. 2007), from data originating from communities of differing socioeconomic status in north and south India. In contrast, there are

few studies available for age at menopause from women in Bangladesh, the country of focus here. In an earlier study, Karim et al. (1985) reported one of the lowest median ages at menopause in the literature at 43.6 years in Bangladesh. These data, however, come from Matlab Thana, a poor socioeconomic area near the capital city of Dhaka, in stark contrast to the affluent middle class women from Sylhet in northeast Bangladesh who are the focus of study in this paper. Table 1 compares age at menopause among various Indian and Bangladeshi populations.

[Table 1 goes about here.]

Given the disparities in wealth between Britain and Bangladesh, Bangladeshi women are particularly appropriate to study with reference to early life development and reproductive function, and against whom to compare healthy white women in the UK. Despite steady improvements in quality of life overall, Bangladesh remains among the poorest of developing nations. From 2000-2009, half of the Bangladeshi population was still below the international income poverty line of US$1.25 per day (http://www.unicef.org) and, in 2010, the country ranked 187th among 198 for its Gross National Income (GNI, nominal, Atlas Method) of US $700, compared to the UK which ranked 31th with a GNI of US $38,200 (http://databank.worldbank.org).

Adding to its economic problems, Bangladesh has a number of ecological features that make it particularly susceptible to the effects of seasonal cyclones and accompanying storm surges that lead to extensive flooding in both rural and urban areas, often with deleterious consequences for population health (Flierl and Robinson 1972; Jakobsen et al. 2006). Much of the country consists of relatively flat alluvial plains created by the deposition of river sediment. Surge and tidal water in the Bay of Bengal act as an obstruction to river flow, making flood situations even more disastrous. Deforestation in the upper watersheds of the Ganges and

Brahmaputra rivers exacerbates flooding downstream. In addition, Bangladesh has shallow coastal waters and a funneling coastline that heightens storm-induced waves (Jakobsen et al, 2006). These ecological features in combination with a population density of 1,142 people / km^2 (ranked as the highest for countries with >10 million inhabitants (http://www.worldatlas.com)) have produced some of the highest mortality figures associated with storm surges in the world (Flierl and Robinson, 1972). In contrast, UK population density is 254 people/km^2 (http://www.worldatlas.com) and cyclones do not usually occur in Britain.

Other health and economic statistics that highlight the differences between Bangladesh and the UK include a lower adult literacy rate in Bangladesh (48% vs. 99%, http://www.indexmundi.com), a higher infant mortality rate (38/1000 in Bangladesh compared to 4.3/1000 in the UK) and a higher adjusted maternal mortality ratio (340 deaths per 100,000 live births in Bangladesh compared to 12 in the UK, http://www.childinfo.org). Current life expectancy in Bangladesh is 60.3 years overall, with 57.6 for males and 63 for women (CIA, 2011). This is in striking contrast to much higher life expectancy for females in developed nations, reflected in UK statistics of 78 years for males and 82 for females (https://www.cia.gov). Finally, one of the earliest population median ages at menopause (43.6 years) comes from Bangladesh (Karim et al. 1985, Table 1) compared to a median age of almost 53 years in the UK (Hardy and Kuh 2005).

Severe cyclones occasionally occur in Bangladesh that cause not only immediate mortality and damage to infrastructure, but also long term damage to agriculture leading to food shortages. This is a serious problem in a country where 82% of the population live in rural areas and depend on agriculture for their subsistence (http://www.unicef.org) compared to only 10% of the population in the UK (http://www.tradingeconomics.com). Mass destruction from severe

cyclones has been of such magnitude in the past that Bangladesh has been unable to recover quickly without aid from other countries. In times of food shortages, women and children -- even among more affluent households -- are most affected as males in the household have priority over the food supply (Karim et al., 1985).

Few studies examine the specific health effects of floods (Ahern et al., 2005), although it would seem that the interaction of malnutrition, crowding, poor sanitation and changes in host-pathogen relationships would raise the incidence of communicable diseases, in turn increasing morbidity as well as mortality (Shears, 1991). Higher numbers of confirmed cases of enterotoxigenic *Escherichia coli*, *Vibrio cholera*, *Shigella* and other pathogens have been reported after floods in Bangladesh (Schwartz et al. 2006; Siddique et al. 1989; Waring and Brown, 2005). There are also increased numbers of fevers, diarrhea and respiratory problems (Cook et al. 2008; Kunii et al. 2002; Seaman 1972). Fu et al (1991) found peaks in rotavirus diarrhea that coincided with a severe flood. Rotavirus diarrhea declined after the flood, but nonrotovirus diarrhea persisted at high levels. Diarrheal diseases account for the majority of deaths after floods, followed by respiratory tract infections; children under age 5 are the most susceptible (Siddique et al., 1991).

Given these environmental conditions in Bangladesh, Núñez-de la Mora and colleagues (2007a, 2008) speculated in recent articles that contrasts in health and sanitation conditions between the UK and Bangladesh might explain differences they observed in reproductive function between sedentee Bangladeshis, Bangladeshi adult migrants to the UK, Bangladeshi child migrants to the UK, and white British women of European descent. For example, they collected retrospective data from migrant and sedentee Bangladeshi women aged 19-35 on their *mother's* age at menopause among other variables (Núñez-de la Mora 2005, pg. 125, Table 14).

Although these data are subject to an unknown amount of recall bias and inaccuracy, Bangladeshi women who migrated to London as adults and women still living in Sylhet reported a comparable age at menopause for their mothers (46.5 years $\pm$ 1.1 SE (n=14) and 47.0 years $\pm$ 1.2 SE (n=27) respectively. In contrast, age at menopause given for the mothers of white women of European origin was significantly higher at 52.4 $\pm$ 0.9 SE years (n=16). Recalled mean age at menarche of Sylheti sedentees (13.1 + 0.2 SE yrs, n=51) also matched that of the adult migrants (12.8 + 0.1 SE, n=58).

Furthermore, the same study also found that those women who had migrated to London as adults shared relatively low salivary progesterone profiles with sedentee women in Sylhet. These profiles overall were significantly lower than those for Bangladeshi women who had migrated as children, second-generation British Bangladeshis who were born in the UK, and white London women of European origin (Núñez-de la Mora et al 2007a). In addition, for those women who had migrated as adults, there was no effect on hormonal levels of amount of time spent in the UK as a migrant. These data strongly suggest, therefore, that the childhood period influences later adult reproductive function. But, a change in environment for middle-class Bangladeshi women during adult life as a result of migration to the UK did not impact either levels of salivary progesterone or the timing of the end of their reproductive lifespan. A number of other studies have also added to our knowledge about the effects of early life development on the ovary, and particularly effects during fetal life and the subsequent two years of infancy and childhood (Coxworth and Hawkes 2010; Cresswell et al. 1997; Hardy and Kuh, 2005).

Given the recent history of Bangladeshi migration to the UK, both child migrants and second-generation women are currently too young to be able to recruit sufficient numbers of women aged >40 for analyses of their ages at menopause. However, data we have collected

from Bangladeshi women aged 35-59 who either migrated to the UK as adults or remained as sedentees in Bangladesh now provide a unique opportunity to examine a number of different variables in early life that could impact age at menopause. These include whether women were born in rural or urban locations, whether they were exposed to cyclones that had devastating consequences in Sylhet during the first two years of life, their relative exposure to a number of infectious and/or parasitic diseases during childhood, their relative nutritional status as measured by adult height, and how well educated they were as children.

In addition to variables that reflect childhood conditions, other factors associated with age at menopause that should be considered across the life course include parity (Cramer et al. 1995; Gold et al. 2001), cycle length (Kaczmarek and Szwed 2001; Whelan et al. 1990), marital status (Sievert et al. 2001); tobacco use (Cramer et al. 1995; Gold et al. 2001; Morris et al. 2012; Reynolds and Obermeyer 2005), levels of education and socioeconomic status (Luoto et al. 1994; Gold et al. 2001; Mishra et al. 2010; Shinberg 1998; Sievert and Hautaniemi 2003). Religion (Hindu/Muslim) is also included as a variable in this study as almost a quarter of Bangladeshi sedentees were Hindus who follow a slightly different diet and lifestyle from Muslims.

We hypothesize here that women who experience more adverse circumstances (e.g., cyclones, disease loads, nutritional stress) during *childhood* will have an earlier age at menopause compared to women not exposed to these circumstances. Secondly, we hypothesize that a change in environment during *adult* life (controlling for factors that might affect the process of reproductive aging across the life course) will not affect age at menopause. From these hypotheses we have generated the following predictions: 1) age at menopause for adult migrants in London and Sylheti sedentees, both of whom spent their childhood years in

Bangladesh, will not differ significantly; 2) age at menopause for both adult migrants in London and Sylheti sedentees will be significantly earlier compared to white women of European descent.

Methods

The majority of Bangladeshi immigrants to London originate from the region and city of Sylhet in northeastern Bangladesh (Eade, 1994); therefore the sedentees were all recruited from Sylhet city. They were recruited with the help of 9 undergraduate students from Shahjalal University in Sylhet, and with assistance from influential community members using personal networks. Only Bangladeshi women with the means to emigrate were included in the study for comparison with immigrants in London (Sievert et al. 2008).

In London, migrants were recruited from community centers with the help of local contacts, and through advertisements in free local papers in boroughs where migrants have settled. About 70% of the migrants who participated in the study lived in the borough of Camden. London women of European origin were recruited from subway stations and market places, through the use of posters in libraries, doctors' surgeries and community centers, and through advertisements in free local papers. All interviews and anthropometric measures of Bangladeshi immigrants in Sylhet and in London were carried out, or supervised closely, by two of the authors (K.B. and T.S.) Almost all interviews were carried out in Bangla (the national language of Bangladesh) or Sylheti (the local dialect in Sylhet).

All women were screened for eligibility in the study by the authors via initial face-to-face interviews, telephone interviews, or emails. Eligibility requirements included being 35-59 years of age, with no use of exogenous hormones in the past 3 months, not pregnant or lactating, and

no history of hysterectomy, oophorectomy, or thyroid problems. The women of European origin were also required of have parents born in the UK or Ireland.

Demographic, reproductive, lifestyle, and anthropometric data were collected during face-to-face interviews from March, 2007 to May, 2010 using a three-part questionnaire with Bangladeshi immigrants (n=174), their London neighbors of European origin (n=154), and Bangladeshi sedentees (n=157). Ethical approval was obtained from the Institutional Review Boards of UMass Amherst, and Ethics Committees at University College London, Durham University, and the M.A.G. Osmani Medical College, Sylhet, Bangladesh.

Women were questioned about their age, birth place, education, financial situation, marital status, migration history, religion, diet, tobacco use, menstrual history, history of child bearing and breast feeding, daily activity patterns, symptoms (e.g., hot flushes or headaches), life stresses, and history of infectious/parasitic diseases. Height, weight, arm circumference, triceps skin fold, waist and hip circumferences were also measured.

Birth registration and hospital births are a recent phenomenon in Bangladesh; therefore we estimated age at interview for some women using a calendar of political events and environmental disasters such as the India-Pakistan War, the Civil War with Pakistan and Bangladeshi Independence, other political events, and major national catastrophes like cyclones, floods, and tidal waves (FAO-UN 2008). Of the 327 Bangladeshi women interviewed, 198 (60%) were certain of their birth date while ages were estimated for the remaining 40% using the Event Calendar.

To estimate age at menopause, women who were no longer menstruating were asked to remember the month and year of their last menstrual period, sometimes with the aid of the Event Calendar (FAO-UN 2008). For comparison within this study, and for comparison across studies,

age at menopause for women living in Bangladesh, Bangladeshi migrants living in London, and women of European descent was calculated as mean recalled age at natural menopause and as median age computed by probit analysis. For the calculation of mean recalled and median ages at menopause, post-menopausal women were defined as those who had not menstruated for at least 12 months (Sievert and Hautaniemi 2003).

Information on cyclone occurrence came from a Storm Surge Modeling document from the Asian Disaster Preparedness Centre (Table II). As cyclones are a common yearly occurrence in Bangladesh, only those categorized as severe cyclones/cyclonic storms, with wind speeds over 88 km/hr, were included in the study (Choudhury, 1992; Islam and Peterson, 2009). The participants were categorized as exposed to cyclones (yes/no) if they were between the ages of 0-2 years or not when a severe cyclone occurred (based on the month of their birth). Although women may have been affected by a cyclone *in utero*, they were not placed in the "yes" group unless they were exposed to a cyclone after birth. This may have an effect of making the age at menopause more similar between the two groups, exposed and unexposed, because women who were exposed *in utero* may be misclassified into the unexposed group. In a second set of analyses, women were included in the exposed group if a severe cyclone occurred from 9 months prior to their birth to 2 years following their birth.

[Table II goes about here.]

For statistical analyses, infectious disease burden was calculated by adding together the number of childhood and infectious diseases the participant reported as ever experiencing in the past. These diseases included chicken pox, mumps, measles, whooping cough, diphtheria, tuberculosis, typhoid, paratyphoid, diarrhea and pneumonia. Infectious disease burden was categorized into 0-2 diseases, 3-4 diseases, and 5+ diseases. Parasite exposure, that is having

had intestinal worms and microbial parasites, was categorized as yes/no. Because of the difference in standard of living between Sylhet and London, level of education was divided into relative, rather than absolute, categories. For Bangladeshis, both migrants and sedentees, levels of education were divided into low (0-6 years), medium (7-9 years), and high (10+ years). For women born in London, levels of education were low (0-10 years), medium (11-14 years), and high (15+ years). Financial situation was assessed by the relative terms of struggling/OK/comfortable/well-off, and religion was categorized as Muslim, Hindu or other. Smoking (in London) or tobacco use in betel quid (among Bangladeshis) was categorized as yes/no.

In each study group, mean ages at menopause were examined by t-test analyses or chi^2 tests in relation to birthplace (urban/rural), place where a woman grew up (urban/rural), potential exposure to a cyclone (yes/no) in childhood (ages 0-8), early childhood (ages 0-2), and *in utero* and early childhood, marital status (yes/no), parity (nulliparity/parous), and tobacco use (yes/no). Analyses of variance were used to examine mean ages at menopause in relation to history of infectious disease burden (1-6), and history of ever having had an intestinal parasite (yes/no), level of education (high/medium/low), financial comfort (4 categories), parity (0, 1-2, 3-4, 5+), length of menstrual cycle at age 20-35 years (< 26 days, 26-32 days, and > 32 days), and religion (Muslim, Hindu, other). Pearson's correlation was used to examine recalled ages at menopause in relation to height, age at first pregnancy, age at menarche, and age at last pregnancy. Among migrants, Pearson's correlation was also used to examine recalled ages at menopause in relation to number of years spent in the UK.

To better understand the consequences of being born in rural or urban circumstances in Bangladesh, urban/rural birthplace was examined in relation to age (for cohort effects), where

the woman said she "grew up," her adult height, number of infectious diseases, having had parasites, potential exposure to cyclones, level of education, and tobacco use.

Cox regression analyses were used to calculate hazard ratios (HR) for the event of not having menstruated for at least 12 months (postmenopausal status). In order to include all women in the analysis, age at most recent menstrual period was entered as the covariate of interest. The first model was limited to sedentee and migrant Bangladeshis. In addition to age at most recent menstrual period, respondent characteristics included migration status, place of birth (urban/rural), potential exposure to cyclones at ages 0-2 (yes/no), infectious disease burden, ever having had parasites, height, education level, financial status, parity, tobacco use, and religion (Muslim/Hindu). While adult height was examined as an indicator of childhood nutritional status, BMI was not included in the model because of the likelihood of changes in weight during and after the menopausal transition.

The second model included Bangladeshi immigrants, sedentees, and Londoners of European descent. In addition to age at most recent menstrual period, respondent characteristics included study group, place of birth (urban/rural), infectious disease burden, ever having had parasites, height, education level (low/medium/high), relative financial status, parity, and tobacco use. Religion (Muslim/Hindu) and cyclone exposure were not included in this model because of the inclusion of the British women of European descent. All analyses were carried out using SPSS 16.0 GP.

Results

Sample characteristics

Significantly more migrants were born in rural areas compared with sedentees and white British women. Potential exposure to cyclones, and history of infectious disease burden and parasites were equally common for both migrants and sedentees, but white British women had significantly lower exposure to infectious diseases and parasites during childhood. Height did not differ significantly between sedentees and migrants, but the white British women were significantly taller in stature compared to both groups of Bangladeshi women (Table III). Migrant Bangladeshi women had a higher BMI, more children, lower educational levels, and were more likely to be struggling financially compared to sedentees and their London neighbors; all of these factors were significantly different across groups. Migrant women were also more likely to be Muslim than sedentees.

[Table III goes about here.]

In analyses comparing rural and urban Bangladeshi women, women born in rural areas were more likely to be older, less educated, shorter in stature, and to have had intestinal parasites/worms compared to women born in urban areas (Table IV). The two groups did not differ in the number of infectious diseases to which they had been exposed during childhood. Women born in rural areas were also more likely to grow up in rural areas. Women were not asked at what age they left their rural birthplace.

[Table IV goes about here.]

Age at menopause

Figure 1 shows the distribution of ages at menopause across the three groups. Mean recalled age at menopause was significantly earlier among Bangladeshi sedentees compared to both Bangladeshi immigrants and London neighbors of European origin (see Table V). A

similar pattern was seen in median ages at menopause computed by probit analysis although here the difference between sedentees and migrants was not significant. The point at which 50% of the sample was menstruating and 50% of the sample was post-menopausal was significantly earlier among Bangladeshi sedentees and migrants compared to Londoners of European origin.

[Figure I and Table V go about here.]

Bivariate Analyses

For all study groups, age at menopause did not vary in relation to some of the early life variables including birthplace (urban/rural), history of infectious disease, history of parasites, age at menarche, and height. However, among sedentee and migrant groups combined, those who were aged 0-2 during the year of a severe cyclone recalled a significantly earlier mean age at natural menopause (45.4 years, s.d. 3.4, n=69) compared to women who were not potentially exposed (47.8 years, s.d. 3.5, n=65, $p<0.001$). No association with menopausal age was found when the age of exposure was expanded to years 0-8. The relationship between exposure to cyclones during ages 0-2 and mean recalled age at menopause held across migrant ($p<0.05$) and sedentee ($p<0.01$) groups when examined separately. The pattern was also the same for women who were aged *in utero* to 2 years during the year of a severe cyclone.

For all study groups, age at menopause did not vary in relation to some later life course variables: length of the menstrual cycle, marital status, level of education, financial comfort, and use of tobacco with betel nut. The length of time that adult migrants spent in the UK did not significantly affect their age at menopause; however, among migrants, age at menopause was significantly associated with parity, increasing with each category from 0 to 5+ ($p=0.016$).

Among sedentees, age at menopause was significantly correlated with age at last birth (r=0.359, p=0.004).

Cox regression analyses

In the first model comparing Bangladeshi sedentees and migrants, an earlier age at menopause was more likely overall among sedentees compared to migrants (HR_{adj} 2.10, 95% CI 1.27 - 3.48). Women born in a rural area were more likely to have a later age at menopause (HR_{adj} 0.54, 95% CI 0.30 - 0.95). There was no significant association between cyclone exposure at ages 0-2 and age at menopause. An earlier age at menopause was more likely among women who had a history of 3-4 (HR_{adj} 1.96, 95% CI 1.26 – 3.05) and 5 or more (HR_{adj} 2.65, 95% CI 1.49 – 4.73) infectious diseases compared to those with a history of 0-2 (P_{trend} = 0.002), but there was no significant association between age at menopause and having had intestinal parasites, or between age at menopause and adult height. Women with low (HR_{adj} 2.61, 95% CI 1.54 – 4.45) and medium (HR_{adj} 2.44, 95% CI 1.20 – 4.95) levels of education were more likely to have a significantly earlier age at menopause compared to those with the highest level of education (P_{trend} = 0.001). A later age at menopause was more likely among women with increasing numbers of children (HR_{adj} 0.88, 95% CI 0.78 – 0.99). Age at menopause was not significantly associated with financial status, tobacco use, or religion. These results are shown in Table VI.

[Table VI goes about here.]

In the second Cox regression analysis that included all three groups of women, a significant risk of an earlier age at menopause was found among Bangladeshi sedentees (HR_{adj} 10.10, 95% CI 4.81-21.00) and migrants (HR_{adj} 4.89, 95% CI 2.48 – 9.61) compared to British women of European descent as shown in Figure II and Table VII. For early life variables, as in

the first model, a later age at menopause was more likely among women born in rural areas (HR_{adj} 0.54, 95% CI 0.35 - 0.84). An early age at menopause was more likely among women with a history of 3-4 (HR_{adj} 1.96, 95% CI 1.34 – 2.87) and 5 or more (HR_{adj} 2.48, 95% CI 1.53 – 4.02) infectious diseases compared to those with a history of 0-2 infectious diseases ($P_{trend} <$ 0.001). A history of intestinal parasites (HR_{adj} 0.67, 95% CI 0.43 - 1.05) approached significance in relation to a later age at menopause (p=0.084). Age at menopause was not associated with height.

For later life variables, an early age at menopause was more likely among women with low (HR_{adj} 2.07, 95% CI 1.32 – 3.23) and medium (HR_{adj} 1.77, 95% CI 1.05 – 2.98) levels of education compared to those with the highest level of education (P_{trend} = 0.005). Increasing numbers of children (HR_{adj} 0.90, 95% CI 0.81 – 1.00) approached significance in relation to a later age at menopause (p=0.059). Age at menopause was not associated with financial status, or use of tobacco.

[Figure II and Table VII go about here.]

Discussion

This study set out to test the hypothesis that women who experience more adverse circumstances during childhood would have an earlier age at menopause compared to women not exposed to these circumstances. From this hypothesis, we predicted that: 1) age at menopause of adult migrants in London and Sylheti sedentees, both of which groups spent their childhood years in Sylhet, Bangladesh, would not differ significantly from each other, and that 2) age at menopause of both these Bangladeshi groups would be significantly earlier than age at menopause for British women of European descent.

Prediction 1

In the findings reported here, mean recalled age at menopause was, in a bivariate analysis, the opposite of our first prediction and was significantly earlier among sedentees (45.8± 3.7 years) compared to migrant Bangladeshi women 47.5 ± 3.3 years). The comparison between median ages at menopause by probit analysis follows a similar pattern (48.1 vs. 49.2 years), but the difference here was not significant. We provide the mean and median ages primarily for comparison with other studies as shown in Table 1. Within each study group, median ages at menopause were later than mean recalled ages at menopause as expected due to methodological differences (Sievert and Hautaniemi 2003). Average ages at menopause are earlier among these upper middle class women in Sylhet compared to women recruited from Matlab, Bangladesh (Karim et al. 1985).

In the first Cox regression analyses, Bangladeshi migrants were more likely to have a later age at menopause compared to sedentees (HR_{adj} 2.10, 95% CI 1.27-3.48). One consideration is that, compared to sedentees, migrants were more often born in rural rather than urban locations (82% vs. 61%). Rural-urban differences in menopausal age have been reported for a number of different populations including those in South India (Table 1) where, in contrast to the study here, women in rural areas (Nirmalan et al. 2004), reported *earlier* ages at menopause compared to those in urban areas (Bairy et al. 2009). A similar difference was shown in Mexico where menopause was earlier among women living in rural communities compared to women living in small cities (Beyene 1986; Canto-de-Cetina et al. 1998; Dickinson et al. 1992); and women in small cities reported an earlier age at menopause compared to women living in large metropolitan areas (Garrido-Latorre et al. 1996; Sievert and Hautaniemi 2003; Velasco et

al. 1990). Other studies have also shown a later age at menopause among urban compared to rural women (e.g., Luoto et al. 1994); however, urban/rural comparisons are generally carried out for residence at time of menopause rather than residence at birth. In the results presented here, we are interested in the influence of early life effects and therefore examined the urban/rural *birthplace* of women, all of whom were currently living in the cities of London or Sylhet and had lived there for varying periods of time. Eighty-four percent of Bangladeshi sedentees and migrants who were born in a rural area also grew up there during childhood.

Closer examination of the Cox regression may explain further the apparently anomalous difference between rural and urban residents in Bangladesh compared to other studies. The unadjusted model shows an increased risk of an earlier menopause (HR_{unadj} 1.42, 95% CI 0.94-2.12) for rural women, consistent with findings from the other studies described above where factors affecting the childhood years have generally not been considered. The adjusted model (HR_{adj} 0.54, 95% CI 0.30-0.95) shows a probable later age at menopause among rural women. This may be because the model accounts for the effects of infectious diseases, education, and other relevant variables in relation to age at menopause. Rural women have more infectious disease (associated with an earlier age at menopause), and lower levels of education (associated with an earlier age at menopause). When these factors are adjusted for, rural women actually have a later age at menopause, consistent with the finding among migrants.

The significant association between lower levels of education and earlier ages at menopause is consistent with other studies (Luoto et al. 1994; Mishra et al. 2010; Shinberg 1998; Sievert and Hautaniemi 2003), as is the association between increasing parity and later ages at menopause (Cramer et al. 1995; Gold et al. 2001). This study is, to our knowledge, the first to show a relationship between an increasing numbers of infectious diseases associated with an

earlier age at menopause. On the other hand, having had parasites or worms was not significantly associated with age at menopause.

We had expected a relationship between potential exposure to cyclones at the early ages of 0-2 and an earlier age at menopause. Cyclones would not directly lower age at menopause, but could create an environment that affects the individual phenotype in early life. The mechanisms for this effect could include disease, nutritional stress or other stressors, such as losing a home or family members (AP, 1972). Historical news reports confirm that Sylhet and surrounding regions experienced flooding and adverse weather conditions during cyclone years (Moraes, 1971; NYT, 1974; Reuters, 1966). Epidemics of cholera, influenza and typhoid were documented in the aftermath of floods in Sylhet in October 1964 (UPI, 1964); and deaths and housing losses followed floods in Sylhet in 1972 (AP, 1972). Resulting food shortages and acute diseases very likely impacted children, particularly girls (Choudhury and Bhuiya 1993; Karim et al. 1985).

The expected relationship between cyclones and age at menopause was supported in the bivariate analyses among Bangladeshi women. Those who were aged 0-2 during the year of a severe cyclone recalled an earlier mean age at natural menopause (45.4 years, s.d. 3.4, n=69) compared to women who were not potentially exposed (47.8 years, s.d. 3.5, n=65, $p<0.001$). However, this finding could be due, in part, to the lack of cyclone exposure at ages 0 to 2 among women born between 1948 and 1960. Women exposed to severe cyclones at ages 0 to 2 had a younger mean age at interview (42.4 vs. 50.7 years). The Cox survival model for age at menopause did not find a significant association for cyclone exposure after controlling for migration status, birth place, education, and other participant characteristics.

Prediction 2

Our second prediction, that age at menopause of sedentees and migrants would be significantly earlier than age at menopause for British women of European descent, is supported by the data. Postmenopausal Bangladeshi women living in both Bangladesh and in London recalled earlier mean ages at natural menopause compared to Londoners of European descent (45.8 (s.d. 3.7) and 47.5 (s.d. 3.3) years vs. 49.1 (s.d. 3.8) years). The same was true using the status quo technique of probit analysis; Bangladeshi women in both Bangladesh and London had a significantly earlier median age at menopause compared to women of European descent (48.1 and 49.2 years vs. 52.8 years). Cox regression analyses for risk of postmenopausal status also indicated an earlier age at menopause among Bangladeshi sedentees (HR_{adj} 10.10, 95% CI 4.81-21.00) and migrants (HR_{adj} 4.89, 95% CI 2.48 – 9.61) compared to Londoners of European descent. As in the first Cox regression, urban/rural birthplace and infectious disease burden was highly significant in relation to age at menopause (table VII) as was education level. In addition, parity and exposure to intestinal parasites approached significance (table VII).

Núñez-de la Mora et al (2007a) had speculated that a heavier disease burden in childhood might explain why comparatively affluent women who grew up in Bangladesh with sufficient nutrition had lower levels of reproductive steroid hormones and an apparently shorter reproductive lifespan. In the Cox regression analyses, an early age at menopause was more likely among Bangladeshi women with a history of 3-4 (HR_{adj} 1.96, 95% CI 1.26 – 3.05) and 5 or more (HR_{adj} 2.65, 95% CI 1.49 – 4.73) infectious diseases compared to those with a history of 0-2 infectious diseases (P_{trend} = 0.001). This significant relationship between infectious disease and an earlier age at menopause remained when Londoners of European descent were included in the model.

We discussed earlier how immunological challenges increase in Bangladesh as a consequence of devastating seasonal floods but, even without such disasters, infectious and parasitic diseases occur at relatively high levels in Bangladesh among all socioeconomic strata. In 1975, for example, Muttalib and colleagues studied a group of students from Dhaka University and found a prevalence rate of 70% for anemia, and 57% for either single or multiple intestinal parasite loads (*Ascaris lumbricoides*, *Entamoeba histolytica* and *Trichuris trichiura*). From our own data, 86% of sedentee and 80% of migrant Bangladeshi women report ever having had intestinal parasites compared to only 19% for the comparative group of white British women (Table III).

How infectious diseases or parasites might ultimately influence age at menopause is unknown but presumably their occurrence in childhood might affect oocyte numbers or the rate of follicular atresia. Cramer et al. (1983) found an earlier age at menopause associated with exposure to the mumps virus. This was explained as a direct effect on ovarian follicular stores; however, other childhood diseases are not known, as yet, to affect the ovary directly. Rather, from a life history perspective, it may be that infectious disease diverts energy away from the maintenance of follicular stores, or affects ovarian function through a change in the hypothalamic-pituitary-ovarian axis. Further research is needed to explore these areas in more detail.

Other studies support the idea of an early life effect on age at menopause as outlined briefly above, although these have mostly focused on early exposures to nutritional stress; differences in nutritional status have long been an explanation for the range of variation in age at menopause across populations (Frisch 1978; Gray 1976). For example, low rates of weight gain *in utero* or during early childhood have been suggested to influence oocyte numbers or the rate

of loss of ovarian follicles, resulting in an earlier age at menopause (Coxworth and Hawkes 2010; Cresswell et al. 1997). In a sample of women aged 60-71 in Hertfordshire, England, age at menopause was earlier among those who had low weight gain during the first year of life (Cresswell et al. 1997). A study of women in Wisconsin found an effect of parental occupation on age at menopause; the daughters of farmers had a later menopause compared with those whose fathers had other occupations. This may be a result of different lifestyle factors including nutrition (Shinberg, 1998). A cohort study of women exposed to caloric restriction during the Dutch famine in 1944-1945 found a younger age at menopause, with early childhood a particularly sensitive age period for that effect (Elias et al. 2003). Similarly, a cohort study of white British women demonstrated a relationship between both low body weight at 2 years, low socioeconomic status during 0-2 years, and an earlier age at menopause (Hardy and Kuh 2002). Furthermore, the longer these women were disadvantaged, the earlier their age at menopause. In a later study, the same authors (Hardy and Kuh 2005) found a cumulative effect of socioeconomic status on age at menopause across the childhood years up until the age of 15, with women in lower social classes throughout childhood having the earliest ages at menopause (52.5 years compared to 53.4 years). From this later study, Hardy and Kuh (2005) speculated that early childhood may be a critical period for determining rates of follicular atresia across a woman's reproductive lifespan.

Height has been used as an indicator of childhood nutrition in relation to age at menopause (Karim et al. 1985). In the study presented here, migrants were significantly taller than sedentees, and Bangladeshis born in urban areas were taller than Bangladeshis born in rural areas; however, there was no significant relationship between height and age at menopause. Likewise, Morris et al. (2012) did not find an association between height and menopausal age in

a study of 21,511 women in the UK. The differences in height between migrants and sedentees may support the supposition that healthier individuals are more likely to migrate (Lassetter and Callister 2009). However, overall, the study populations in London and Sylhet were matched for levels of affluence: only those groups with the means to migrate to the UK were included in the study. All of the women in our sample originated from relatively well-off, middle class families in Bangladesh.

Conclusion

Our findings here highlight the importance of early life effects and particularly infectious disease loads in influencing age at menopause relative to factors that occur later in the life course (Hardy and Kuh, 2002; Mishra et al 2010). Place of birth and migration status, along with infectious disease burden, and levels of education were the most significant factors influencing age at menopause. Rural-urban birthplace was also important, and serves as a proxy for how birthplace affected exposure to other environmental factors during childhood.

Increased parity and higher levels of education increased the likelihood for a later menopause. Both of these findings concur with other studies. One of the most significant later lifestyle factors known to accelerate age at menopause is smoking (Cooper et al, 1999; Cramer et al, 1995; Lutterodt et al., 2009; Reynolds and Obermeyer, 2005; Soares and Melo, 2008) but, in this study, tobacco use was not associated with age at menopause. It may be that the chemical effect of tobacco differs when delivered by smoking rather than by betel quid tucked between the cheek and gum (Núñez-de la Mora et al. 2007b).

As stated earlier, age at menopause is dependent on the number of oocytes with which a woman is endowed during fetal life, as well as the rate of loss of these oocytes during the life

course through the process of atresia. Existing evidence points to inter-individual variation in the numbers of oogonia and follicles that develop *in utero* (Block, 1953; Forabosco et al., 1991; Lutterodt et al., 2009), which are dependent on maternal condition and other environmental factors. The initial endowment of oocytes *in utero,* however, does not necessarily program women for an early or late menopause (Ginsberg 1991); subsequent conditions during childhood and even later in life may be potentially equal or more important influences. Among these, the burden of infectious diseases and how it affects allocation of resources among growth, maintenance and reproduction, may be a significant factor affecting the length of the reproductive lifespan.

Acknowledgements: We are especially thankful for the help of Susmita Paul Jamy, Sunali Biswas, Nusrath Jahan, Mahbuba Bari Shikder, Shamima Begum, Sayema Islam Shetu, Sufia Sultana, Rumana Begum, Kanij Fathema, Salma Begum, Khaza Nazim Uddin, Tamanna Sultana, Eva Goldwater, and for the help of the women in London and Sylhet, Bangladesh who participated in this study of age at menopause.

Literature Cited:

Ahern M, Kovats RS, Wilkinson P, Few R and Matthies F. 2005. Global health impacts of floods: Epidemiologic evidence. Epidemiol Rev 27:36-46.

AP. 1972. At least 50 Reported Dead From Floods in Bangladesh. New York Times Jun 26: 18.

Bairy L, Adiga S, Bhat P, Bhat R. 2009. Prevalence of menopausal symptoms and quality of life after menopause in women from South India. Aust N Z J Obstet Gynaecol 49:106-9.

Beyene, Y. 1986. Cultural significance and physiological manifestations of menopause: a biocultural analysis. Cult Med Psychiatry. 10:47-71.

Block E. 1953. A quantitative morphological investigation of the follicular system in newborn female infants. Acta Anatomica. 17:201-206.

Broekmans FJ, Soules MR and Fauser BC. 2009. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465-93.

Bukovsky A. 2010. How can female germline stem cells contribute to the physiological neo-oogenesis in mammals and why menopause occurs? Microsc Microanal. 16:1-9.

Canto-de-Cetina, T.E., Canto-Cetina, P., Polanco-Reyes, L. 1998. Encuesta de sintomas del climaterio en areas semirurales de Yucatan. Revista de Investigacion Clinica. 50:133-135.

Childinfo Statistics for maternal mortality ratios, retrieved 6/4/12 http://www.childinfo.org/maternal_mortality_countrydata.php

Choudhury AM. 1992. Cyclones and the coastal zones of Bangladesh, The Bangladesh Quarterly, Dept. of Films and Publications.

Choudhury AY and Bhuiya A. 1993. Effects of biosocial variables on changes in nutritional status of rural Bangladeshi children, premonsoon and post-monsoon flooding, J Biosoc Sci 25:351-357.

CIA World-Factbook, retrieved 6/4/12. https://www.cia.gov/library/publications/the-world-factbook/fields/2102.html

Cook A, Watson J, van Buynder P, Robertson A and Weinstein P. 2008. 10th Anniversary Review: Natural disasters and their long-term impacts on the health of communities, J Environmental Monitoring 10:167-175.

Cooper GS, Sandler DP and Bohlig M. 1999. Active and passive smoking and the occurrence of natural menopause, Epidemiol 10:771-773.

Coxworth JE, Hawkes K. 2010. Ovarian follicle loss in humans and mice: lessons from statistical model comparison. Hum Reprod 25(7):1796-805.

Cramer DW, Harlow BL, Xu HJ, Fraer C and Barbieri R. 1995. Cross-sectional and case-controlled analysis of the association between smoking and early menopause, Maturitas 22:79-87.

Cramer DW, Welch WR, Cassells S and Scully RE. 1983. Mumps, menarche, menopause and ovarian cancer. Am J Obstet Gynecol 147:1-6.

Cresswell JL, Egger P, Fall CHD, Osmond C, Fraser RB and Barker DJP. 1997. Is the age of menopause determined in-utero? Early Hum Dev 49:143-148.

Databank Worldbank GNI list, retrieved 6/4/12
http://databank.worldbank.org/databank/download/GNIPC.pdf

Data.UN mortality rate for children UK, retrieved 6/4/12
http://data.un.org/Data.aspx?d=MDG&f=seriesRowID%3A561

Dickinson F, Castillo T, Vales L, Uc L. 1992. Migration, socio-economic status and age at menarche and menopause in the Yucatan, Mexico. International J Anthro 10(1):21-28.

Eade J. 1994. Identity, Nation and Religion – Educated Young Bangladeshi Muslims in London East-End, International Sociol 9:377-394.

Elias SG, van Noord PAH, Peeters PHM, den Tonkelaar I and Grobbee DE. 2003. Caloric restriction reduces age at menopause: the effect of the 1944-1945 Dutch famine. Menopause 10:399-405.

FAO-UN. 2008. Food and Agricultural Organization of the United Nations. Guidelines for Estimating the Month and Year of Birth of Young Children. FAO, Rome, Italy.

Flierl GR, Robinson AR. 1972. Deadly Surges in the Bay of Bengal-Dynamics and Storm-tide Tables. Nature 239:213-215.

Forabosco A, Sforza C, De Pol A, Vizzotto L, Marzona L, Ferrario VF. 1991. Morphometric study of the human neonatal ovary. Anat Rec. 231:201-208.

Frisch RE. 1978. Population, food intake, and fertility. Science 199:22-29.

Fu B, Unicomb L, Rahim Z, Banu NN, Podder G, Clemens J, Van Loon, FPL, Rao MR, Malek A and Tzipori S. 1991. Rotavirus-associated diarrhea in rural Bangladesh: two-year study of incidence and serotype distribution, J Clin Microbiol 29:1359-63.

Garrido-Latorre, F., Lazcano-Ponce, E. C., Lopez-Carrillo, L., Hernandez-Avila, M. 1996. Age of natural menopause among women in Mexico city. International J Gynecol Obstet 53:159-166.

Ginsberg J. 1991. What determines the age at the menopause? BMJ 302:1288-9.

Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD and Skurnick J. 2001. Factors Associated with Age at Menopause in a Multiethnic Sample of Midlife Women, Am J Epidemiol 153:865-874.

Gray RH. 1976. The menopause – epidemiological and demographic considerations. In Beard RJ (ed). The Menopause: A Guide to Current Research and Practice. Baltimore: University Park Press, pp.25-40.

Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR and Klein NA. 2008. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause, Hum Reprod 23:609-708.

Hardy R and Kuh D. 2002. Does early growth influence the timing of the menopause? Evidence from a British birth cohort, Human Reproduction 17:2474-2479.

Hardy R, and Kuh D. 2005. Social and Environmental Conditions Across the Life Course and Age at Menopause in a British Birth Cohort Study, BJOG 112:346-354.

Henderson KD, Bernstein L, Henderson B, Kolonel L and Pike MC. 2008. Predictors of the timing of natural menopause in the multiethnic cohort study, Am J Epidemiol 167:1287-1294.

Islam T and Peterson RE. 2009. Climatology of landfalling tropical cyclones in Bangladesh 1877-2003. Natural Disasters 48:115-135.

Jakobsen F, Azam MH, Ahmed MZ, and Mahboob-Ul-Kabir M. 2006. Cyclone storm surge levelsalong the Bangladeshi coastline in 1876 and 1960-2000. Coastal Engineering Journal 48:295-307.

Johnston SL. 2001. Associations With Age at Natural Menopause in Blackfeet Women, Am J Hum Biol 13:512-520.

Kakkar VK, Kaur D, Chopra K, Kaur A and Kaur IP. 2007. Assessment of the variation in menopausal symptoms with age, education and working/non-working status in north-indian sub population using menopause rating scale (MRS). Maturitas 57:306-314.

Karim A, Chowdhury AKMA, and Kabir M. 1985. Nutritional status and age at secondary sterility in rural Bangladesh. J Biosoc Sci 17:497-502.

Kapur P, Sinha B, and Pereira B. 2009. Measuring climacteric symptoms and age at natural menopause in an Indian population using the Greene Climacteric Scale, Menopause 16:378-384.

Kaczmarek M, Szwed A. 2001. Age at menopause and reproductive determinants in Polish women. Anthropological Review 64:57-72.

Kriplani A and Banerjee K. 2005. An overview of age of onset of menopause in northern India. Maturitas 52:199-204.

Kunii O, Nakamura S, Abdur R and Wakai S. 2002. The impact on health and risk factors of the diarrhea epidemics in the 1998 Bangladesh floods, Public Health 116:68-74.

Lassetter JH, Callister LC. 2009. The impact of migration on the health of voluntary migrants in western societies. J Transcult Nurs 20:93-104.

Luoto, R., Kaprio, J., Uutela, A. 1994. Age at natural menopause and sociodemographic status in Finland. Am J Epidemiol 139:64-76.

Lutterodt MC, Sørensen KP, Larsen KB, Skouby SO, Andersen CY, Byskov AG. 2009. The number of oogonia and somatic cells in the human female embryo and fetus in relation to whether or not exposed to maternal cigarette smoking. Hum Reprod. 24:2558-66.

McKinlay S, Thompson B and Jefferys M. 1972. Investigation of age at menopause. J Biosoc Sci 4:161-173.

Mishra GD, Cooper R, Kuh D. 2010. A life course approach to reproductive health: theory and methods. Maturitas. 65:92-7.

Moraes D. 1971. East Pakistan: The Wave; The wave, New York Times Jan 10: 26.

Morris DH, Jones MK, Schoemaker MJ, McFadden E, Ashworth A, Swerdlow AJ. 2012. Body mass index, exercise, and other lifestyle factors in relation to age at natural menopause: analyses from the breakthrough generations study. Am J Epidemol 175(10): Epub ahead of print

Muttalib MA, Islam N, Ghani JA, Khan K, Azizullah A, Islam B. 1975. Intestinal parasites in University of Dacca students. J Trop Med Hyg. 78(10-11):224-6.

Nirmalan PK, Katz J, Robin AL, Ramakrishnan R, Krishnadas R, Thulasiraj RD, Tielsch JM. 2004. Female reproductive factors and eye disease in a rural south Indian population: the Aravind Comprehensive Eye Survey. Invest Ophthalmol Vis Sci 45:4273-6.

Nunez-de la Mora A. 2005. Developmental effects on adult reproductive hormone levels: a migrant study. Unpublished PhD Dissertation, University of London, Department of Anthropology, London.

Núñez-de la Mora A, and GR Bentley 2008 Early life effects on reproductive function. In Trevathan WR, Smith EO, and McKenna JJ (eds) New Perspectives on Evolutionary Medicine, eds. Oxford University Press, New York, pp.149-168.

Núñez-de la Mora A, Napolitano D, Uddin F, Choudhury O, and G.R. Bentley. 2007b. Betel nut use among first and second generation Bangladeshi women in London, UK, and women resident in Bangladesh. J of Immigr Minor Hlth 9:299-306.

Núñez-de la Mora A, RT Chatterton, O. Choudhury, D. Napolitano, and G.R. Bentley. 2007a. Childhood conditions determine adult progesterone levels. PLOS Med 4:e167.

NYT. 1974. Aid limited by shortage of food and transport, New York Times Aug 18: 3.

Pandit D, Prabha R, Shanbhag S, Mayekar R. 2005. Morbidity pattern of women attending screening program in an urban slum in Mumbai. Indian J Comm Med 30(4):134-5.

Piplai C. 1991. Age at menopause of Tamang women tea-labourers of Jalpaiguri district, West Bengal, India. International J Anthropol 6(4):233-6.

Reuters. 1966. Storm Kills 18 in Pakistan, New York Times Jun 11: 40.

Reynolds RF, Obermeyer CM. 2003. Correlates of the age at natural menopause in Morocco, Annals Hum Biol 30:97-108.

Reynolds RF, and Obermeyer CM. 2005. Age at Natural Menopause in Spain and the United States: Results from the DAMES Project, Am J Hum Biol 17:331-340.

Sakata R, Shimizu Y, Soda M, Yamada M, Hsu W-L, Hayashi M, Ozasa K. 2011. Effect of radiation on age at menopause among atomic bomb survivors. Radiation Research; 176:787-795.

Schwartz BS, Harris JB, Khan AI, Larocque RC, Sack DA, Malek MA, Faruque ASG, Qadri F, Calderwood SB, Luby SP, et al. 2006. Diarrheal epidemics in Dhaka, Bangladesh, during three consecutive floods: 1988, 1998, and 2004. Am J Tropical Med Hygiene 74:1067-73.

Seaman JA. Relief Work in a Refugee Camp for Bangladesh Refugees in India. 1972. Lancet 2:866-870.

Shears, P. 1991. Epidemiology and infection in famine and disasters, Epidemiology and Infection 107: 241-251.

Shinberg, D. S. 1998. An event history analysis of age at last menstrual period: correlates of natural and surgical menopause among midlife Wisconsin women. Soc Sci Med. 46(10):1381-1396.

Siddique, AK, Islam Q, Akram K, Mazumder Y, Mitra A and Eusof A.1989. Cholera Epidemic and Natural Disasters-Where is the Link, Tropical and Geographic Medicine 41:377-382.

Siddique AK, Baqui AH, Eusof A and Zaman K. 1988. Floods in Bangladesh: pattern of illness and causes of death, J Diarrhoeal Dis Res. 1991;9:310-4.

Sievert LL. Menopause A Biocultural Perspective. 2006. New Brunswick: Rutgers University Press.

Sievert LL, Waddle D and Canali K. 2001. Marital status and age at natural menopause: Considering pheromonal influence, Am J Hum Biol 13:479-485.

Sievert LL, Begum K, Sharmeen T, Chowdhury O, Muttukrishna S and Bentley G. 2008. Patterns of occurrence and concordance between subjective and objective hot flashes among Muslim and Hindu women in Sylhet, Bangladesh, Am J Hum Biol 20:598-604.

Sievert LL, and Hataniemi SI. 2003. Age at menopause in Puebla, Mexico. Hum Biol 75:205-226.

Soares SR, Melo MA. 2008. Cigarette smoking and reproductive function. Curr Opin Obstet Gynecol 20:281-91.

Stolk et al. 2012. Meta-analyses identify 13 loci associated with age at menopause. Nature Genetics 44:260-8.

te Velde ER, Scheffer GJ, Dorland M, Broekmans FJ and Fauser BCJM. 1998. Developmental and Endocrine Aspects of Normal Ovarian Aging. Molecul Cell Endocrinol 145:67-73.

Thomas F, Renaud F, Benefice E, De Meeus T and Guegan JF.2001. International Variability of Ages at Menarche and Menopause: Patterns and Main Determinants, Hum Biol 73:271-290.

Trading economics rural population UK, retrieved 6/4/12.
http://www.tradingeconomics.com/united-kingdom/rural-population-percent-of-total-population-wb-data.html

UNICEF Bangladesh statistics, retrieved 6/4/12
http://www.unicef.org/infobycountry/bangladesh_bangladesh_statistics.html

UPI. Pakistanis Report Cholera Toll, New York Times, Oct 12, 1964. pg. 6.

Velasco, E., Malacara, J. M., Cervantes, F., de Leon, J. D., Davalos G., Castillo J. 1990. Gonadotropins and prolactin serum levels during the perimenopausal period: correlation with diverse factors. Fertil Steril. 53(1):56-60.

Waring SC and Brown BJ. 2005. The threat of communicable diseases following natural disasters: a public health response, Disaster Manag Response 3:41-47.

Whelan, E. A., Sandler, D. P., McConnaughey, D. R., Weinberg, C. R. 1990. Menstrual and reproductive characteristics and age at natural menopause. Am J Epidemiol. 131:625-632.

Worldatlas population density, retrieved 6/4/12
http://www.worldatlas.com/aatlas/populations/ctypopls.htm

Worldbank, crude death rates, retrieved 6/4/12
http://data.worldbank.org/indicator/SP.DYN.CDRT.IN

Table 1: Age at menopause among women in Bangladesh and India

Age at menopause (years)	Method and sample size	Population characteristics	Source
Bangladesh			
43.6	Life table analysis 3-year prospective data N=2324, aged 15-50	14 villages in Matlab, Bangladesh, 76% with no formal education, 89% Muslim, 40% husbands worked in agriculture	Karim et al. 1985
India			
42.56	Mean recalled age at menopause N=174 women aged 35+	Urban slum, Dharavi, Mumbai, 67% Hindu, 30% Muslim, 52% illiterate, 32% tobacco use (mishri, paan, gutkha, sniffing)	Pandit et al. 2005
43.4 ±3.9	Mean recalled age at menopause N=1841 postmenopausal women, aged 40-85	Southern India, Madurai, Tirunelveli and Tuticorin districts, random cluster sampling of a rural population	Nirmalan et al. 2004
46.82	Median by probit analysis N=129, aged 30-65	Northern India, state of Uttarakhand, 97% Hindu, 73% middle class housewives	Kapur et al. 2009
47.3 ±2.3	Mean recalled age at menopause N=64, aged 38-55	Tamang tea-laborers in the Jalpaiguri district of West Bengal, India, migrants (n=22), first (n=27), and second (n=15) generation	Piplai 1991
48.7 ±2.3	Mean recalled age at menopause N=208, aged 35-65	Northern India, urban setting of SSA Nagar, Mohali, recruited from a menopause clinic, 80% completed high school, 54% employed	Kakkar et al. 2007
48.7	Mean recalled age at menopause N=352 postmenopausal women	Southern India, patients at an outpatient Ob/Gyn clinic in Udupi, Authors noted better SES and health care in this region of India	Bairy et al. 2009
Mean 46.7 ±4.7 Median 48	Mean and median recalled ages at menopause N=201 postmenopausal women	Northern India, women who accompanied patients to a tertiary referral health center, 68% illiterate, 70% vegetarian 90% Hindu, 64% middle and high SES	Kriplani and Banerjee 2005

Table II: Severe cyclonic storms experienced in Bangladesh 1948-75.

Date	Deaths	Damages
17-19 May 1948	1,200	Loss of 20,000 cattle
15-20 November 1950	Not reported	Not reported
16-19 May 1958	Not reported	Loss of 14,500 cattle And standing crops
21-24 October 1958	12,000	100,000 homes destroyed
25-29 May 1960	106	Not reported
10-11 October 1960	6,000-11,446	62,725 homes and 380km^2 of crops destroyed
30-31 October 1960	8,149	Loss of 27,793 cattle and 568,161 homes
6-9 May 1961	11,468	Loss of 25,000 cattle and damages to the railroads
27-30 May 1961	10,466	Not reported
28-29 October 1962	50,000	Loss of cattle
28-29 May 1963	11,520	Loss of 32,617 cattle, 376,322 homes and many crops
5-8 June 1963	Not reported	Not reported
25-29 October 1963	Not reported	Not reported
10-11 May 1965	19,270	Not reported
14-15 December 1965	870	Not reported
1 October 1966	850	1.5 people million affected, 65,000 cattle lost
12 December 1966	Not reported	Not reported
11 October 1967	Not reported	Not reported
23-24 October 1967	128	Not reported
5-7 May 1970	18	Not reported
12-13 November 1970	300,000	Loss of >1 million cattle and >400,000 homes
16-18 November 1973	Not reported	Not reported
6-9 December 1973	183	Not reported
24-28 November 1974	20	Loss of 1,000 cattle and 2,300 homes
9-12 May 1975	5	Not reported

Sources: Chronology of major cyclones and storm surges in Bangladesh (compiled from Murty et al., 1986; Khalil1992; and Murty and El-Sabh1992).

Table III: Comparisons of early life and later life characteristics

	Sedentee Bangladeshi N=157	Migrant Bangladeshi N=174	p-value across 2 groups[a]	Women of European Origin N=154	p-value across 3 groups[b]
Early Life					
Mean age in years (s.d.)	46.77 (7.12)	46.39 (7.28)	0.634	47.94 (6.82)	0.126
Birthplace (%)					
Rural	61	82.2		34.4	
Urban	39	17.8	<0.001	65.6	<0.001
Cyclone exposure 0-2yrs	47.80%	50.60%	0.6	n/a	n/a
Mean number of infectious diseases	3.05 (1.50)	3.09 (1.30)	0.819	3.27	0.283
Number of Infectious Diseases					
0-2	37.6	31.6		28.6	
3-4	45.2	56.3		59.1	
5+	17.2	12.1	0.114	12.3	0.130
Ever had parasites or worms (%)	86	79.9	0.142	18.8	<0.001
Mean Height in cm (s.d.)	151.74 (5.57)	152.93 (5.75)	0.058	162.46 (7.04)	<0.001
Education Level (%)					
Low	65	84.5		27.9	
Medium	30.6	10.9		31.8	
High	4.5	4.6	<0.001	40.3	<0.001
Age at menarche in yrs (s.d.)	13.2 (1.35)	13.0 (1.27)	0.898	12.8 (1.95)	0.076
Later Life					
Cycle length (%)					
<26 days	7.8	5.7		6.5	
26-32 days	86.4	90.8		77.3	
>32 days	5.8	3.4	0.424	5.8	0.660
Mean parity (s.d.)	3.20 (1.75)	3.75 (1.72)	0.003	1.08 (1.30)	<0.001
Mean BMI (s.d.)	26.16 (4.11)	27.29 (3.19)	0.005	25.46 (4.79)	<0.001
Financial Status (%)					
Struggling	11	38.5		24.7	
OK	38.1	36.8		49.4	
Comfortable	29.7	21.8		22.1	
Well off	21.3	2.9	<0.001	2.6	<0.001
Tobacco use (%)	40.5	36.3	0.11	19.0	<0.001
Religion (%)					
Muslim	77.4	100		n/a	
Hindu	21.9	0		n/a	
Other	0.6	0	<0.001	n/a	n/a

[a] Comparison across 2 Bangladeshi groups; [b] Comparison across sedentee, migrant, and white London groups

Table IV: Comparison of characteristics between sedentees and migrant Bangladeshi women born in rural and urban areas of Bangladesh

	Rural N=237	Urban N=91	P value
Mean age at interview in years (s.d.)	47.5 (7.1)	44.4 (6.8)	<0.001
Environment in which she grew up			
Rural	84.0%	3.3%	
Urban	16.0%	96.7%	<0.001
Potential exposure to a cyclone between the ages of birth-2 years	65.0%	73.6%	0.149
Mean height at interview in cm (s.d.)	151.7 (5.6)	154.2 (5.6)	<0.001
Mean number of infectious diseases (s.d.)	3.2 (1.4)	2.9 (1.4)	0.100.
Ever had intestinal parasites/worms	85.7%	74.7%	0.019
Level of education			
Low	51.5%	12.1%	
Medium	16.5%	8.8%	
High	32.1%	79.1%	P<0.001
Uses tobacco	38.8%	30.8%	0.265

Table V: Age at natural menopause among sedentees, Bangladeshi migrants, and London women of European origin

Group	N	Mean recalled (s.d.)	N	Median by probit analysis (95% Fieller Bounds)
Sedentee Bangladeshi (SB)	69	45.8 (3.7)[a]	157	48.1 (47.0-49.3)[b]
Migrant Bangladeshi (MB)	65	47.5 (3.3)[a]	172	49.2 (48.0-50.4)[b]
European origin (EO)	44	49.1 (3.8)[a]	154	52.8 (51.7-53.9)[b]

[a]SB < EO p<0.001 [b]SB < EO p<0.001
[a]SB < MB p<0.01 [b]MB < EO p<0.01
[a]MB < EO p<0.05

Table VI: Cox survival model for age at menopause among Bangladeshi sedentees and migrants

	Unadjusted HR	**Adjusted HR**	**95% Confidence interval**	**P-value**	**P trend**
Sedentees and Migrants					
Migrants (ref)					
Sedentees	1.41	2.10	1.27-3.48	0.004	
Birth Place					
Urban (ref)					
Rural	1.42	0.54	0.30-0.95	0.033	
Cyclone exposure age 0-2	1.27	1.19	0.81-1.74	0.376	
Infectious Disease Burden					
0-2 (ref)					0.002
3-4	1.54	1.96	1.26, 3.05	0.003	
5+	1.94	2.65	1.49, 4.73	0.001	
Ever had parasites/worms					
No (ref)					
Yes	0.79	0.64	0.36-1.12	0.119	
Height	0.98	0.97	0.94-1.01	0.11	
Education Level					
Low	1.17	2.61	1.54-4.45	<0.001	
Medium	1.26	2.44	1.20-4.95	0.013	0.001
High (ref)					
Financial Status					
Struggling	0.75	1.13	0.55-2.33	0.739	
OK	0.75	0.82	0.42-1.59	0.558	
Comfortable	0.86	0.98	0.53-1.81	0.94	
Well off (ref)					0.644
Mean parity	0.96	0.88	0.78-0.99	0.038	
Tobacco use					
No (ref)					
Yes	1.09	0.98	0.64-1.45	0.874	
Religion					
Muslim (ref)					
Hindu	1.21	1.03	0.55-1.94	0.923	

Table VII: Cox survival model for age at menopause among Bangladeshi sedentees, migrants and London women of European origin

	Unadjusted HR	**Adjusted HR**	**95% Confidence interval**	**P-value**	**P-trend**
Study group					
White British (ref)					
Sedentees	3.52	10.1	4.81-21.00	<0.001	
Migrants	2.37	4.89	2.48-9.61	<0.001	
Birthplace					
Urban (ref)					
Rural	1.14	0.54	0.35-0.84	0.006	
Infectious Disease Burden					
0-2 (ref)					
3-4	1.32	1.96	1.34-2.87	<0.001	
5+	1.44	2.48	1.53-4.02	0.048	<0.001
Ever had parasites/worms					
No (ref)					
Yes	0.998	0.67	0.43, 1.05	0.084	
Height	0.97	0.99	0.96-1.02	0.511	
Level of education					
Low	1.41	2.07	1.32-3.23	0.001	
Medium	0.93	1.77	1.05-2.98	0.031	
High (ref)					0.005
Financial Status					
Struggling	0.67	1.11	0.59-2.08	0.742	
OK	0.73	1.06	0.60-1.85	0.848	0.822
Comfortable	0.72	0.89	0.51-1.56	0.678	
Well off (ref)					
Mean parity	1.11	0.90	0.81-1.00	0.059	
Tobacco use					
No (ref)	1.42	1.07	0.75-1.51	0.71	
Yes					

Figure Legends:

Figure I: Recalled ages at natural menopause for European British, migrant Bangladeshis, and sedentee Bangaldeshis (n=178)

Figure 2: Hazard function for age at menopause European British, migrant Bangladeshis, and sedentee Bangladeshis (n=485)

Figure I: Recalled ages at natural menopause for European British, migrant Bangladeshis, and sedentee Bangaldeshis (n=178)

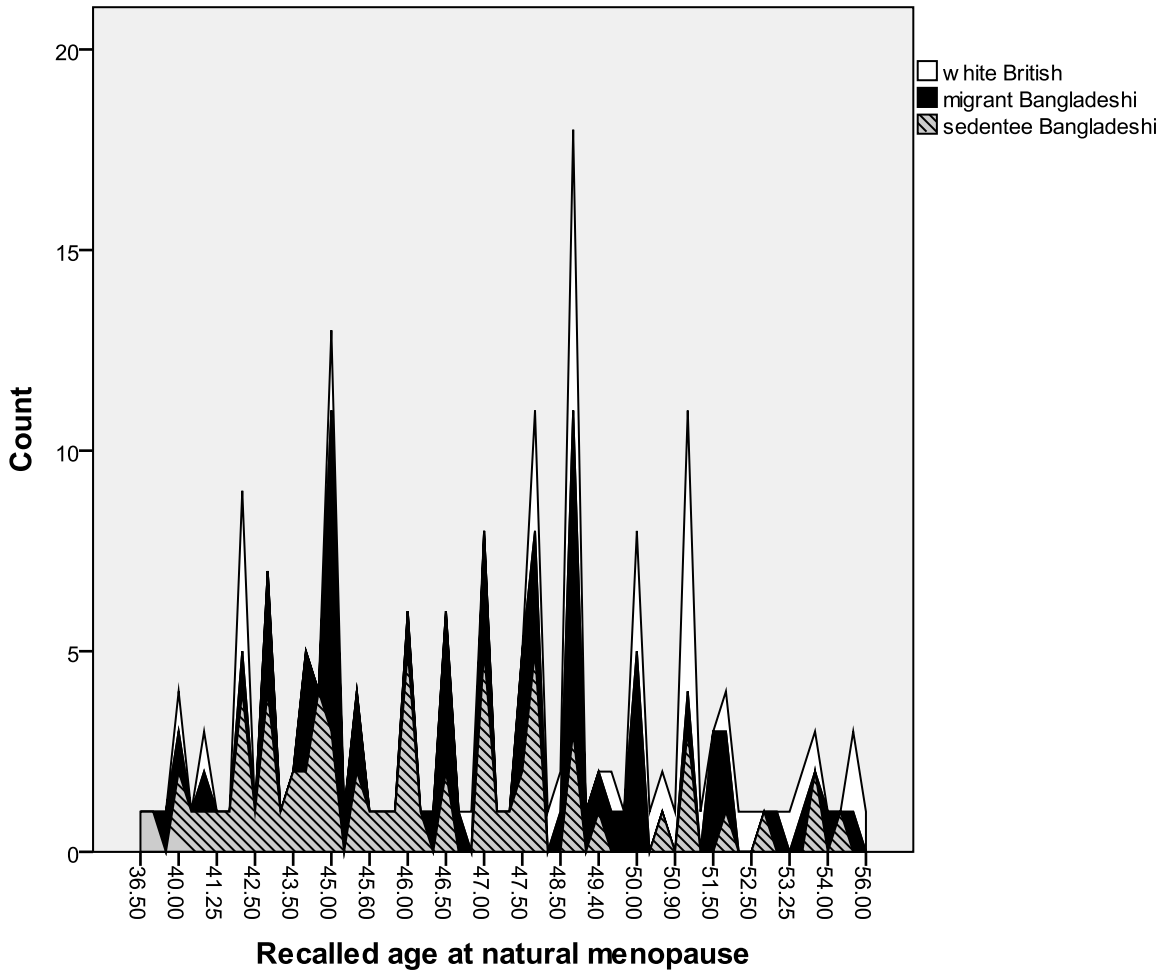

Figure II. Hazard function of age at menopause for European British, migrant Bangladeshis and sedentee Bangladeshis (n=485)