

Review Article

Reproduction and Lifespan: Trade-offs, Overall Energy Budgets, Intergenerational Costs, and Costs Neglected by Research

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ABSTRACT In human females allocation of resources to support reproduction may cause their insufficient supply to other metabolic functions, resulting in compromised physiology, increased risks of diseases and, consequently, reduced lifespan. While many studies on both historical and contemporary populations show that women with high fertility indeed have shorter lifespans. This relationship is far from universal: a lack of correlation between fertility and lifespan, or even an increased lifespan of women with high fertility have also been documented. Reduced lifespan in women with high fertility may be undetectable due to methodological weaknesses of research or it may be truly absent, and its absence may be explained from biological principles. I will discuss the following reasons for a lack of the negative relationship, described in some demographic studies, between the number of children and lifespan in women: (1) Number of children is only a proxy of the total costs of reproduction and the cost of breastfeeding is often higher than the pregnancy cost but is often not taken into account. (2) Costs of reproduction can be interpreted in a meaningful way only when they are analyzed in relation to the overall energy budget of the woman. (3) Trade-offs between risks of different diseases due to reproduction yield different mortality predictions depending on the socio-economic status of the studied populations. (4) Costs of reproduction are related not only to having children but also to having grandchildren. Such intergenerational costs should be included in analysis of trade-offs between costs of reproduction and longevity. *Am. J. Hum. Biol.* 21:524–532, 2009. © 2009 Wiley-Liss, Inc.

THE PRINCIPLE OF ALLOCATION

It is not easy to maintain positive energy balance and good health by individuals living in poor environments, with inadequate diets, intense workloads, and high burden of diseases. Energy and nutrients from dietary intake are used to support physiological maintenance (i.e., all physiological processes, such as immune function, renewal of tissues, neutralization of toxins, digestion) and physical activity. In children and adolescents growth processes require additional energy and nutrients. Reproduction adds additional costs and makes the task of surviving even more challenging. Costs of reproduction are higher for human females than for males due to energetic and nutritional requirements of pregnancy and lactation, and traditionally female-dependent childcare. Costs of pregnancy result from fetal growth, growth and maintenance of maternal supporting tissues, and maternal fat accumulation (Blackburn and Loper, 1992). Energetic demands of lactation are a consequence of milk synthesis and the maintenance of metabolically active mammary glands (Lunn, 1994).

If resources are limited, allocation to one function can only occur at the expense of other functions (Zera and Harshman, 2001). Competition for common resources results in trade-offs among life history traits. Since reproduction is costly, but essential, the costs of reproductive effort must be paid. Increased allocation to current reproduction should result in reduced future reproduction and/or reduced lifespan. Pregnancy and lactation take energy and nutrients away from other processes, and some physiological and metabolic functions may, therefore, be negatively affected by the reproductive effort. Repeated reproductive events may negatively affect maternal health, especially at older age and, ultimately, lead to earlier death.

REPRODUCTION AND LONGEVITY

The question about the impact of reproduction on longevity has been addressed by numerous epidemiological and historical demography studies (for review see Le Bourg, 2007). Epidemiological research is more often concerned with documenting the differences in health and mortality between nulliparous and parous women, rather than with quantifying the relationship between the number of children and lifespan. Often, these studies are conducted in modern populations from developed countries, and, therefore, are not able to include women with high parity. On the other hand, these studies are usually able to collect information about potentially confounding factors, such as, for example, socioeconomic status or breastfeeding. Such information is often not available in studies relying on historical demography data, but the advantage of these studies results from the fact that they include women who have large number of children, and, therefore, bore significant costs of reproduction.

A U-shaped relationship between the number of children and risk of mortality was described by several studies (Green et al., 1988; Lund et al., 1990; Manor et al.,

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2000). For example, in the contemporary Israeli population the lowest mortality risk was observed for women with two children, while women with no children and those with more than two had higher mortality (Manor et al., 2000). In the historical Swedish population (1766–1885) the number of children ever born by a woman had a negative impact on maternal longevity (Dribe, 2004). Giving birth to four or more children increased maternal mortality by 30–50% in comparison to women with fewer children. Having four or five children, instead of none or one, shortened the woman's lifespan by 3.5 years. The studied population consisted of four groups of rural families, differing in economic status, and further analyses showed that the described relationship between fertility and mortality was restricted only to landless women. Women from families of crown or noble tenants, or semilandless, who had better socio-economic status, were not affected by reproductive costs at all.

Similarly, in a historical population of northwest Germany (1720–1870), the number of children had a negative impact on longevity but only for the group of poor, landless women (Lycett et al., 2000). Among other women, with higher economic status, a positive relationship between the number of children and longevity was described. These data suggest that trade-offs between costs of reproduction and longevity apply only for those women for whom such costs are a substantial part of their overall energy budget.

Gender of children may also be an important variable to consider when analyzing the relationship between costs of reproduction and longevity. Having sons may be more energetically expensive for mothers than having daughters. Boys have faster rate of intrauterine growth and heavier average size at birth (Loos et al., 2001; Marsal et al., 1996) and, given larger body size, perhaps higher lactational demands (Hinde, 2007). Women have longer interbirth intervals after giving birth to a son, than after giving birth to a daughter (Mace and Sear, 1997), and offspring born after brothers have lower birth weight (Cote et al., 2003), lower height at adulthood (Rickard, 2008) and also lower number of surviving children (Rickard et al., 2007) than those born after sisters. These results suggest that the maternal organism may become more depleted by producing male offspring.

In Finnish Sami (Helle et al., 2002) and a Flemish village (Van de Putte et al., 2003), sons decreased maternal lifespan, while daughters did not. In four Polish small agricultural villages, however, analyses of parish records from 1886 to 2002 showed that both the number of sons and the number of daughters decreased maternal lifespan, and did so to the same degree (Jasienska et al., 2006a). Each additional son or daughter decreased maternal lifespan by 95 weeks, or almost two years, on average. Such costs of reproduction seem very high, but women in this population, in addition to costs of reproductive events, faced high costs of physical labor. It is also likely that they had low lifetime estrogen levels (a potential importance of this in relation to the impact of fertility on lifespan will be discussed later in this article) due to relatively poor nutritional status they had in utero and intense workload they experienced through life (Jasienska and Ellison, 1998; Jasienska and Ellison, 2004; Jasienska et al., 2006b,c).

By contrast, a number of studies of historical populations documented a positive association between the

number of children and longevity, as, for example, in the Amish population (McArdle et al., 2006), and German women of higher socio-economic status (Lycett et al., 2000). Similarly, in a French–Canadian cohort of women (17th and 18th century), longevity increased with increasing number of children, especially for women with the late age at last birth (Muller et al., 2002), and this finding may be thought as evidence for slower rate of ovarian and overall aging (Dribe, 2004). However, other studies did not find either positive or negative significant relationships between number of children and longevity of mothers (for example, Le Bourg et al., 1993).

ENERGETIC COSTS OF MENSTRUAL CYCLE AND PREGNANCY

Reproduction in the human female requires energy to maintain ovarian and uterine function, but this maintenance is not very energetically expensive: during several days of the luteal phase of the cycle an increase of 6–12% in the resting metabolic rate has been reported in some women (Bisdee et al., 1989; Curtis et al., 1996; Meijer et al., 1992). An average basal metabolic rate for a woman from an industrialized country is 1,300 kcal/day (Leonard, 2008), thus the increase due to menstrual cycle is between 70 and 150 kcal/day. To meet these additional expenses, women tend to increase their caloric intake during the late luteal phase (Johnson et al., 1994). This evidence points to the fact that some additional energy beyond the regular metabolic needs is required to support regular menstrual function (Strassmann 1996a,b). These costs, however, are negligible in comparison to the much higher and longer lasting energetic demands of pregnancy and lactation.

For well-nourished women from industrialized countries, the estimated costs of pregnancy constitute an expense of an extra 90, 290, and 470 kcal a day, respectively, for the first, second, and third trimesters (Butte and King, 2005). During the last trimester, the woman may require up to 22% of additional energy over the pre-pregnant values (Butte et al., 1999).

COSTS NEGLECTED BY RESEARCH ON REPRODUCTION AND LONGEVITY: LACTATION AND CHILDCARE

Basic calculations of energetic costs of reproduction in women can be based on the total costs of all pregnancies and on cumulative costs of lactation. The cost of lactation is a very important variable in calculations of total reproductive costs because, on average, one day of lactation places higher demands on maternal energetics than one day of pregnancy. Costs of lactation change with the age of the infant (Rashid and Ulijaszek, 1999) and the frequency of daily feedings, but, on average, lactation requires additional 626 kcal per day (Butte and King, 2005) and may last for a few years. Calculations of lifetime costs of reproduction for two women: European aristocrat born in the 18th century (Tillyard, 1994) and Polish rural agriculturalist born in the early 20th century illustrate the importance of including costs of lactations (Jasienska, in preparation). The aristocratic woman gave birth to 22 children and the woman from the Polish village to 12 children.

The total cost of pregnancy for a woman with a mean weight gain during gestation of 12 kg is ~77,150 kcal (Butte and King, 2005), and thus the lifetime energetic costs of pregnancies was about 1,697,000 kcal for the aristocrat and about 926,000 kcal for the agriculturalist. When it comes to the lifetime energetic costs of breastfeeding, they were zero for the aristocrat (since all her children were wet-nursed) and about 2,479,000 kcal for the agriculturalist (assuming 12 months of breastfeeding per each child, as reported by women in villages from the Mogiëlica Human Ecology Study Site (Jasienska unpublished), and taking into account the fact that one of her children died shortly after birth). Total lifetime energetic costs of reproduction were 1,697,000 kcal for the aristocrat and twice as high, at 3,405,000 kcal, for the agriculturalist.

Lifetime costs of lactation are usually not taken into account by research analyzing relationships between fertility and longevity of women. While it is understandable that data on duration of breastfeeding for individual women are not available from historical demographic records, omissions of these costs may significantly bias the results of research on reproduction and longevity. Errors may be substantial when women from different socio-economic classes are compared, since it is likely that there was a considerable variation in breastfeeding behavior among such groups.

In addition to direct costs of pregnancy and lactation, there are also often significant indirect costs which are associated with childcare or with an increase in intensity and duration of work to obtain resources necessary to support the family (Sujatha et al., 2000). Estimates of these costs are hard to find as well. Women who do not have any additional help clearly spend more time and energy providing for each additional child. However, as children grow older they are able to provide childcare to younger siblings, and become involved in housework, agricultural work, or work for wages (Biran et al., 2004; Kramer 2002; Nag et al., 1978). Therefore, the relationship between the number of children and the maternal costs of childcare is clearly not linear.

THE INTERGENERATIONAL COST: CHILDREN AND GRANDCHILDREN

Children not only impose biological costs but also provide some benefits to their parents. They contribute labor to the household and, in preindustrial societies, were especially important for elderly parents, given the absence of pensions system or health insurance (Tsuya et al., 2004). How children affect parental longevity depends on economic conditions and the social structure of the population, especially family structure, and behavioral patterns of taking care of aging parents. In the Liaoning province in China between 1749 and 1909, women had 12% higher mortality if they did not have any living sons (Campbell and Lee, 2004). For widows with no sons, mortality in older age was 55% higher than for women who had at least one son and a living husband. By comparison, having living sons did not have any effect on mortality of older males, unless those males were widowers. If the male had no wife and no son, his chances of dying increased by 54% comparing to males who had a wife and at least one son. Having children had a positive effect on parental life

expectancy also in some historical European communities (Tsuya et al., 2004).

It is likely that longevity of parents is not only influenced by costs and benefits resulting from interactions with their children, but in later years, also with their grandchildren. Traditionally, many older people lived and, in some societies still do, with one of their children and his or her offspring. Costs and benefits of such interactions are important to consider when discussing health and mortality risks. Grandmothers were shown to be important in several societies. In historical Germany (Volland and Beise, 2002) and Japan (Jamison et al., 2002), the presence of the maternal grandmother was associated with increased survival of her grandchildren. In the Hadza hunter-gatherers of Tanzania, grandmothers seem to increase the nutritional status of grandchildren (Hawkes et al., 1997) and both nutritional status and survival in the rural Gambia (Sear et al., 2000).

While the impacts of grandparents on health and survival of grandchildren are widely studied, another question is whether these interactions have any effect on the wellbeing of grandparents themselves. In patrilineal systems, cost and benefits of interactions with grandchildren may be different for grandmothers and grandfathers. Grandfathers may not be expected to contribute much to the household, while expectations toward grandmothers may be much higher and may include childcare or physical labor (Pashos, 2000). In times of economic hardships, grandfathers may feel entitled to a higher share of resources than those left for grandmothers, and some studies report higher incidence of malnutrition in older females than in older males (Aliabadi et al., 2008). Family often inherits land or property from males and not females (Varley, 2007), and therefore old males are treated with more care and respect. Even in some matrilineal societies, like in the Tonga from Gwembe Valley of rural Zambia, older women are left without any wealth, while men can accumulate enough to support themselves well into old age (Cliggett, 2005, 65–66). Grandmothers are expected to provide more care and support to families even in modern environments, as shown, for example, by a study investigating roles of grandparents in support networks in neonatal intensive care units in Scotland (McHaffie, 1992).

Furthermore, costs related to interactions with grandchildren may vary for maternal and paternal grandmothers. Maternal grandmothers, according to the concepts of kin selection and paternity uncertainty (Hamilton, 1964), are expected to contribute more toward children of their daughters than to children of their sons, and many studies show that maternal grandmothers are indeed the primary care givers (Euler and Weitzel, 1996; Michalski and Shackelford, 2005; Sear and Mace, 2008). In some societies, like in rural Ethiopia, where maternal grandmothers have beneficial effect on child's condition and survival, grandmothers relieve their daughters of heavy domestic labor rather than directly helping with childcare (Gibson and Mace, 2005). Several studies documented benefits for grandchildren living with maternal grandmothers and lack of such benefits when children live with their paternal grandmothers (Hawkes et al., 1997, 1998; Jamison et al., 2002; Sear et al., 2000; Volland and Beise, 2002). It is very likely that providing such benefits for children is not cost-free for their grandmothers. Childcare and resource acquisition are energetically demanding

and may negatively affect nutritional status of grandmothers.

REPRODUCTIVE COSTS AND THE OVERALL ENERGY BUDGETS

Even if total costs of reproduction based on costs of pregnancy, lactation, and childcare have been calculated, this is just part of the story when attempting to assess the impact of lifetime costs of reproduction on maternal health and longevity. When female zebra finches are forced to pay high costs of reproduction by laying more eggs, they do not seem to suffer negative metabolic consequences, provided that their diets are supplemented (Bertrand et al., 2006). It is likely that the same is true for human females. High costs of reproduction will not have the same effects on women who have good diets and low levels of physical activity, as on women in poor energetic condition.

Basal metabolism, measured by basal metabolic rate (BMR), is expected to rise in women who are pregnant or nursing a child. The BMR of a pregnant woman should increase during each of the four quarters of pregnancy, respectively, by about 3, 7, 11, and 17% above the pre-pregnant values (Hyttén and Leitch, 1971). Empirical data usually support these theoretical predictions, but only in women who have good nutritional status (Butte et al., 1999; Durnin, 1991, 1993; Lunn, 1994; Prentice and Prentice, 1990; Prentice and Whitehead, 1987). In Swedish women, for example, BMR was elevated from the very beginning of the pregnancy (Prentice and Whitehead, 1987). However, when the environmental conditions do not provide adequate energy, the physiology of women who are already pregnant or lactating may be forced to rely on special energy-saving strategies in order to support energetic demands of the child (Peacock, 1991). One of the mechanisms which allows for reallocating more energy to reproduction is reduction in the maternal basal metabolism (Peacock, 1991; Prentice et al., 1989; Prentice et al., 1995).

In women from Scotland and Gambia, who are in worse nutritional condition, not only did the BMR increase but it showed a significant decrease up to the 12th week of pregnancy. BMR of those women approached the pre-pregnant values as late as the 22–26 week and continued to rise further, but even at delivery it was still much lower than the BMR of Swedish women (Prentice and Whitehead, 1987). Pregnant Nigerian women showed significant variability in BMR, which corresponded to variability in their nutritional status (Cole et al., 1989). Even well-nourished Western women show significant variation in the BMR responses to pregnancy paralleling differences in their pre-pregnant body fat (Prentice et al., 1989). In fact, maternal adipose reserves serve as highly significant predictors of changes in the BMR (Bronstein et al., 1996). Reduction in the BMR at the beginning of pregnancy is therefore an important strategy for women in poor nutritional condition. Lowering the BMR considerably reduces energetic costs of pregnancy and allows women to allocate some energy into fat storage which may be critical for the energetic support of lactation.

Lactation is predicted to cause, on average, a 12% increase in the BMR above the nonpregnant values (Hyttén and Leitch, 1971), but the BMR does not always increase according to the theoretical predictions. During

lactation, the BMR has been observed to increase, decrease, or remain at pre-pregnant levels (Forsum et al., 1992; Goldberg et al., 1991; Guillermo-Tuazon et al., 1992; Lawrence and Whitehead, 1988; Madhavapeddi and Rao, 1992; Piers et al., 1995). Variation in the BMR responses also here can be explained by differences in the nutritional status of the women studied (Prentice and Prentice, 1990). Women from the Gambia during the first year of lactation showed a 5% decrease in the BMR compared to the pre-pregnant values (Lawrence and Whitehead, 1988). The authors of this study calculated that this small reduction in BMR saves about 200 kcal a day and, in comparison to women who increased their BMR during lactation, savings add up to about 380 kcal a day. The saved energy can be allocated into synthesis of milk and help the mother who has low energy intake to energetically support the growing child. The savings from the reduction of the BMR, although not sufficient to cover the whole expense of breast-feeding, are still substantial, since the average daily cost of milk production for women in developing countries is about 840 kcal (Lunn, 1994).

Reduction in basal metabolism indicates that some of the metabolic processes (e.g., components of the maintenance metabolism, like protein turnover or immune function) are temporarily slowed down or even halted (King et al., 1994; Prentice and Whitehead, 1987). A long-term reduction in the BMR is, therefore, not likely to be neutral and may be detrimental to the maternal health.

NEGATIVE IMPACT OF REPRODUCTION ON HEALTH: OBESITY, DIABETES, CARDIOVASCULAR DISEASES, AND OSTEOPOROSIS

Reproduction requires not only additional energy but also nutrients. In addition, physiological and metabolic adjustments associated with pregnancy may cause permanent changes in the maternal organism, especially when pregnancies are numerous. Self-reported health status, a reliable predictor of mortality (Idler and Benyamini, 1997), is lower for women with at least three pregnancies, and especially for women with six or more pregnancies, after adjusting for age, ethnicity, education, marital status, household income, and wealth (Kington et al., 1997). In well-nourished women, parity is positively related to the risk of obesity, impaired glucose tolerance, non-insulin-dependent diabetes, and cardiovascular diseases.

Cardiovascular diseases, diabetes, and obesity

Many studies documented a positive relationship between the number of children and an increased risk of cardiovascular diseases. The longitudinal Framingham Heart Study and the National Health and Nutrition Examination Survey documented a positive relationship between the number of pregnancies and the subsequent development of cardiovascular disease (Ness et al., 1993). In British women with at least two children, each additional child increased the risk of coronary heart disease by 30% (Lawlor et al., 2003). Risk became lower, but still statistically significant, after adjustment was made for obesity and metabolic risk factors. In addition, having gone through six or more pregnancies increased the woman's risk of all types of strokes by 70% (Qureshi et al., 1997).

In women, particularly in those from economically developed countries, an increase in the number of children increases the risk of being overweight or obese. Body weight is gained during each pregnancy, and most women keep at least some of this weight after the delivery (Harris and Ellison, 1997). In a large study of U.S. women, each birth was associated with a 0.55 kg of permanent increase in body weight (Brown et al., 1992), while other studies reported that maternal body weight increased by 0.4–3.0 kg after each pregnancy (Harris and Ellison, 1997). Among women with parity of three or more, a higher proportion was overweight than in women with lower parity. In American women from Utah, a dose-response relationship was observed between the number of children and risk of obesity (Bastian et al., 2005): each additional live birth increased the risk of obesity by 11%.

In contrast, in women from developing countries, the relationship between parity and obesity is often very different. Repeated reproductive events cause a reduction of body weight and body fat. The maternal depletion syndrome refers to the long-term negative changes in the maternal nutritional status, as opposed to the short-term changes associated with a single pregnancy or breastfeeding (Winkvist et al., 1992). In Papua New Guinea, the nutritional status of women decreased with parity (Garner et al., 1994). This maternal depletion occurred even though birth intervals were relatively long (three years on average) in this population. Women gained only about 5 kg of weight during pregnancy which means that weight gain from fat was very low. The authors estimated that fat deposition, blood and extracellular volume expansion together contributed only about 650 gm to the weight gain. In Turkana from northwestern Kenya, women from both nomadic and settled populations had parity-related decline in fat reserves (Little et al., 1992). In another African population, the !Kung San, higher number of surviving children was related to lower body weight in women, while in men those with more surviving children had higher body weight (Kirchengast, 2000).

Improvement in socioeconomic status seems to increase the maternal ability to resist the stress of repeated reproductive events. In Papua New Guinea, the earlier mentioned decline in nutritional status was substantial in women who were foraging horticulturalists, while such changes were not observed among wage earners (Tracer, 1991). Changing the lifestyle from nomadic to settled improved nutritional status of Rendille Kenyan women after they had moved to a large city (Shell-Duncan and Yung, 2004). In contrast, the Rendille women still leading nomadic life showed parity-related decreases in BMI and fat reserves. Well-nourished Toba women from Argentina, a population undergoing a continuing transition from seminomadic hunter-gatherer to a sedentary, periurban lifestyle did not lose excess weight gained during pregnancy despite prolonged and intense breastfeeding (Valeggia and Ellison, 2003).

The risk of diabetes, closely linked to obesity, may increase with parity as well. Among rural Australian women, those with five or more children had 28% higher risk of diabetes than women with three or four children, and 35% higher risk than women with one or two children (Simmons et al., 2006). In Finnish women, parity of 5 or higher was related to 42% higher risk of diabetes compared to the average risk experienced by women in this population (Hinkula et al., 2006). Some studies showed

increased risk of diabetes in childless women (Simmons, 1992), suggesting that this may be the reason that other studies, which included such women, did not show a linear relationship between parity and risk of diabetes.

Bone density and osteoporosis

It can be hypothesized that women who had high number of pregnancies and breastfed their children would have lower bone mineral density, and, therefore, higher risk of osteoporosis in later life. During pregnancy and lactation high levels of calcium are required to support the child's developing skeleton. Such high calcium requirements are often met by mobilization of calcium from the skeleton of the mother (Prentice, 2000). Each pregnancy causes 3–4.5% decrease of bone mineral density in the lumbar region (Black et al., 2000; Drinkwater and Chestnut, 1991). Bone mineral density is regarded as reliable predictor of bone strength (Karlsson et al., 2005), and a decrease of about 10% of initial density doubles the risk of fractures in women (Cummings et al., 1995). Lumbar bone density decreases further by 3–6% during lactation (Karlsson et al., 2001; Laskey and Prentice, 1997). In comparison, post-menopausal women lose about 1–3% per year of bone mineral content at the spine and hip (Prentice, 2000).

Changes in bone density occurring during pregnancy and lactation are reversible (Karlsson et al., 2005; Laskey and Prentice, 1997), at least in women from industrialized populations, and there seems to be no consistent relationship between the number of children and bone mineral density of the mother in older age (Bererhi et al., 1996). Of course the absence of such relationships may be due to a rather low fertility of women from industrialized countries. A large study in Italy, with over 40,000 participants, did not show any effects of having children on bone density, but it compared women who never had a full-term pregnancy to women who only had one or two children (De Aloysio et al., 2002).

Because estrogen has positive effect on bones, the number of menstrual cycles during which estrogen is produced should be positively related to bone mineral density (Somner et al., 2004). Estrogen deficiency plays a crucial role in the development of osteoporosis (Raisz, 2005). Bone mineral density is positively related to the number of reproductive years, that is, the period from menarche to menopause. In natural fertility populations, women who have high parity also have longest reproductive lifespans. Early menarche and late menopause increase the total time during which women can become pregnant.

Furthermore, early menarche and late menopause, and high number of children should all be positively related. One can expect all these characteristics to be present in women who are in a good nutritional status. Good nutritional status is related to early reproductive maturation, which by itself adds a few years to the total time during which a woman can conceive. In addition, early-maturing girls have higher levels of reproductive hormones in their cycles than girls who mature later, and this difference persists for at least several years past the menarche (Vihko and Apter, 1984). Women who are in good nutritional status for most of their adult lives have cycles with high levels of hormones. High levels of hormones lead to increased probability of conception (Lipson and Ellison, 1996; Venners et al., 2006), and therefore increased parity. Therefore, in women who are in good condition, a negative

effect of high parity on bone density may be not detectable, since it is counter-balanced by the effect of having many high-estrogen cycles which is beneficial for bone health. Indeed, the protective effect of parity on hip bone mineral density is shown in a study on Amish women with high parity (7.6 live births on average) (Streeten et al., 2005). In these women, parity correlated positively with the later age at menopause and higher cumulative estrogen exposure (calculated as the age at menopause minus the age at menarche). Furthermore, a positive effect of parity on bone density disappeared in statistical analysis when body mass index (BMI) of the woman was taken into account. In this group of Amish women, a positive trend of increasing BMI with increasing parity was detected, i.e., women who had most children also had high BMI. Women with higher BMI may have higher levels of estrogens in post-menopausal years. Fat tissue is the most significant source of estrogen after the menopause. Adrenal glands secrete androstenedione—the androgen steroid hormone which is converted to estrogen by the enzyme aromatase in the adipose tissue. Overweight women have more adipose tissue, and therefore benefit from higher levels of estrogen in post-menopausal years (Bray, 2002) that promote higher bone density (Alden, 1989; Nguyen et al., 1995).

TRADE-OFFS BETWEEN HIGH COSTS OF REPRODUCTION AND LOWER RISKS OF REPRODUCTIVE CANCERS

Cumulative costs of reproduction are related to an increased risk of cardiovascular diseases, diabetes, and strokes even in women who are in good nutritional status. Why then do not all studies show an increased mortality in women who have high number of children? Some studies show even a decreased risk of mortality in women with high parity, which seems like a paradox. These contradictory results may be explained by the fact that same features of reproductive life which involve the highest metabolic and physiological costs of reproduction, i.e., early beginning and high fertility, may also serve a protective function, leading to decreased mortality from certain diseases.

Early age at first reproduction and high number of children are the most important factors protecting women against breast cancer and other reproductive cancers (Hinkula et al., 2001; Kvale, 1992; MacMahon, 2006; Mettlin, 1999). Breast cancer risk is also decreased by breastfeeding. Unfortunately, short term, not-exclusive (i.e., when maternal milk is supplemented by other foods) lactation, commonly practiced by women in economically developed countries, may not have as beneficial, protective effect (Kvale, 1992; MacMahon, 2006). It can, therefore, be hypothesized that for women from developing countries breastfeeding may lead to a more pronounced reduction in breast cancer risk than for women from economically developed countries. For example, in women from Nigeria the risk of breast cancer decreased by 7% per each 12 months of breast-feeding (Huo et al., 2008) and in women from India by more than 9% (Gajalakshmi, 2000). In women from developing countries, breastfeeding has a suppressive effect on ovarian function, delaying resumption of ovarian activity after pregnancy, because feeding sessions are more frequent than in developed countries and mothers are often in relatively poor nutritional state. Breastfeeding leads to ovarian suppression especially when mothers nurse babies often during the day (Konner

and Worthman, 1980). In the !Kung hunter-gatherers, nursing episodes occur as often as every 15 min and high nursing frequency is related to low levels of estradiol and progesterone. But even such frequent nursing is unlikely to cause long-lasting ovarian suppression when the mother is in a good nutritional condition (Valeggia and Ellison, 2004). For these reasons (low frequency of nursing and good nutritional condition), women from economically developed countries, even when they are breastfeeding for a long period of time, experience a much earlier resumption of ovarian activity.

While many studies documented a protective effect of pregnancies against the risk of reproductive cancers, a recent study from Finland is unusual because it included a very large number of women of very high parity and reliably diagnosed causes of death (Hinkula et al., 2006). The study included almost 88,000 women with parity of 5 or higher (grand multiparity, GM), out of which 3,678 women had at least 10 deliveries. Death rates for GM women were compared to average death rates for the Finnish female population (standardized mortality ratio). GM women had 11% lower mortality from all cancers. Mortality from breast cancer was 36% lower and 32% lower in the case of uterine and ovarian cancers.

Therefore, trade-offs between costs resulting from reproduction and benefits from reducing risk of reproductive cancers are important to consider when attempting to understand a relationship between reproduction and longevity in women. These trade-offs are not the same in all populations. The risk of breast cancer results from high, lifetime exposure to estrogens (Bernstein, 2002; Jasienska et al., 2000; Key and Pike, 1988). Each reproductive event suppresses menstrual cycles, and early pregnancy, by inducing the differentiation of breast tissue, reduces its susceptibility to neoplastic transformation (i.e., development of tumors) (Balogh et al., 2006). In addition, the post-pregnancy period is characterized by low levels of endogenous estrogens, and it is thought that this may further suppress potential tumor growth.

In poor agricultural societies, however, women generally have low levels of estrogen and progesterone in menstrual cycles. Nutritional shortages and intense labor periodically suppress ovarian function and, in addition, postpone the age of sexual maturation, when cycles begin (Jasienska, 2001, 2003; Jasienska and Ellison, 1998, 2004; Panter-Brick and Ellison, 1994; Panter-Brick et al., 1993). Poor developmental conditions during fetal and childhood periods are also related to lower hormone levels in adult women (Jasienska et al., 2006b,c; Nunez-de la Mora et al., 2007). Therefore, women in poor populations have low lifetime exposure to estrogens. In contrast, in economically well-off populations, women have high levels of hormones in menstrual cycles and only rarely experience ovarian suppression (Ellison et al., 1993). Many of the historical genealogies analyzed, in the context of impact of fertility on longevity, were based on data from well-off families. High fertility in women from such families significantly reduced lifetime exposure to estrogen. Estrogen exposure in women living in poor conditions is low to begin with, and high fertility has, therefore, a much lower impact on reducing lifetime estrogen levels.

WHEN DOES REPRODUCTION REDUCE LIFESPAN?

While there is convincing evidence that reproduction is costly and related to long-term changes in female physiolo-

TABLE 1. Comparative costs and benefits of reproduction and their impact on health and lifespan in women with the same, high parity, but differing in socio-economic status^a

	Poor women	Well-off women
Energetic costs of pregnancies	High	High
Energetic costs of lactations	High	Low/None
Nutritional ability to meet costs of pregnancy and lactation	Low	High
Levels of estrogen in menstrual cycles	Low	High
Risk of maternal depletion	High	Low
Risk of obesity	Low	High
Risk of cardiovascular diseases	Increased	Increased
Risk of strokes	Increased	Increased
Risk of diabetes	Increased	Increased
Risk of osteoporosis	Not affected	Not affected
Risk of breast cancer	Slightly reduced	Greatly reduced
Risk of uterine and ovarian cancers	Slightly reduced	Greatly reduced
Lifespan	Reduced	Not affected/Increased

^aIn well-off women, reproduction increases risks of several diseases, but these risks are offset by significant reduction in risk of breast and other reproductive cancers. In poor women, reproduction increases risks of the same diseases, but these women have low lifetime risks of breast and reproductive cancers due to low levels of hormones in menstrual cycles, even when they are not reproducing. In addition, in poor women, energetic and nutritional expenses of reproduction cannot be easily compensated and may cause more substantial damage to the maternal organism.

ogy, by no means should a negative impact of reproduction on lifespan be always expected (Table 1). Energetic and metabolic costs of reproduction cannot be calculated just by adding up all of the woman's children. Women with a similar number of children may differ in costs of lactation and this difference can be very substantial. Similarly, they may differ in their ability to meet energetic costs of reproduction, due to differences in lifestyle, dietary intake, and physical activity. High costs of reproduction and negative effects on some aspects of health may be outweighed by positive effects on other health dimensions. The lifestyle maintained by women is an important factor to consider, as for some women intense reproduction will substantially reduce their risks of reproductive cancers, while for other women risks of these cancers are relatively low, even when they do not have many children. Indirect costs of reproduction, such as those paid by grandmothers taking care of grandchildren, may also change the overall lifetime ratio of costs and benefits of reproduction.

Therefore, in women from rich environments high fertility may not translate into reduction in longevity for several reasons. The costs of pregnancies are often not accompanied by costs of lactations, or these costs are very low. In many European populations, women who had higher socio-economic status were not expected to nurse their children at all and wet-nurses were commonly employed. In well-off women, even if they nurse their children, the costs of pregnancy and lactation are easily met by additional energy intake, especially when there are no energetic demands from physical activity. Furthermore, there are trade-offs between reproductive costs and benefits provided by protection against breast cancer. It is even possible that in well-off women benefits may outweigh costs and high fertility may, in fact, be related to lifespan extension. Finnish grand-multiparity women had higher mortality from all metabolic diseases, especially diabetes and cardiovascular diseases, than the average for the population, but these risks were clearly outweighed by lower mortality from cancers, since their overall mortality was

slightly lower than the population average (Hinkula et al., 2006). Among women with at least 10 births, however, the overall mortality was increased. While they had lower mortality from reproductive cancers, their mortality from cardiovascular diseases and diabetes was much higher.

A negative relationship between fertility and longevity may, therefore, be expected in women who due to multiple pregnancies and breastfeeding not only pay high costs of reproduction but also when these costs cannot be easily compensated by increases in dietary intake and reduction in physical activity. The most pronounced negative relationship between reproduction and lifespan should be expected when the lifestyle (poor nutrition and high work demands) of the woman leads to low lifetime estrogen levels, and additional reduction in these levels caused by reproductive events is relatively insignificant.

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