UNIVERSITY OF CALIFORNIA, SAN DIEGO

Physical Activity and Metabolic Physiology in Postmenopausal Women: An Evolutionary Approach

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Anthropology

by

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The Dissertation of Andrew W. Froehle is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

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DEDICATION

For Andrea

EPIGRAPH

We don't stop playing because we grow old;

we grow old because we stop playing.

-attributed to George Bernard Shaw

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ABSTRACT OF THE DISSERTATION

Physical Activity and Metabolic Physiology in Postmenopausal Women: An Evolutionary Approach

by

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Doctor of Philosophy in Anthropology

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Humans diverge from our close relatives (chimpanzees/bonobos) in high survivorship to menopause and decades of postmenopausal longevity. Evolutionary perspectives see the human postmenopausal lifespan as a species-typical life history trait that has evolved by selection for maintenance of physiological systems at increasingly older ages. Maintenance of body composition and low rates of metabolic and cardiovascular disease should thus characterize the early postmenopausal period, which they do in hunter-gatherers despite little access to Western medicine.

In contrast, women in industrialized society tend to increase body fat and have high rates of metabolic syndrome during the early postmenopausal period; as such, the prevailing medical view is that menopause itself increases disease risk. Physical activity relates to metabolic health, and may help explain this disparity: older hunter-gatherers tend to be highly active, while women in industrialized society tend to be increasingly sedentary with age.

Within the framework of evolutionary medicine, the present study investigates the effects of physical activity on body composition and resting energy expenditure (REE) in postmenopausal women from San Diego. Low REE, low fat-free mass and high body fat are risk factors for metabolic syndrome; exercise may increase fat-free mass and REE, and lower body fat. Long-term, habitually-active women were compared to sedentary women who completed a 16-week training program. In this sample, active women tended to have less body fat, but did not have higher fat-free mass or REE. Despite strength and aerobic fitness gains, the training program failed to increase fat-free mass and REE.

Comparison of this study's subjects to published results from highly-trained athletes and data on hunter-gatherers suggests that even the active women in the present sample were rather sedentary, consistent with the idea of an intensity threshold for the effects of exercise on metabolism. Additionally, the training program's lack of effect is consistent with some past studies, supporting the idea that the metabolic response to exercise is muted with age and sedentary behavior. Thus, both the intensity and timing of exercise may be important to reducing metabolic disease risk, possibilities that can be evaluated by continuing to study postmenopausal health from the perspective of evolutionary medicine.

CHAPTER 1: INTRODUCTION

Menopause marks the permanent cessation of ovulation and the complete elimination of fecundity, arising from the confluence of two key life history characteristics. The first is semelgametogenesis, common to most female birds and mammals, where oocyte production occurs on a limited basis only early in life and results in a finite number of eggs (Finch, 1990; Peccei, 2001b; Ellison, 2010; males, meanwhile, are iterogametogenic, maintaining the capacity for germ cell division late into adult life: Bribiescas, 2006). Limited oocyte supplies alone, however, do not necessarily result in menopause: the second necessary factor is a lifespan of sufficient length to outlast the reserve of eggs.

In humans, oocyte production occurs during gestation, the number of egg cells peaking during the fifth month and declining thereafter to a population of approximately one million at birth. Ovulation and apoptosis cooperate to deplete this store, accelerating with age (Faddy et al., 1992; Hansen et al., 2008) and eventually reaching a threshold of ~1000 surviving ova. These few remaining oocytes produce very little estradiol-17β, which plays an important role in stimulating uterine wall preparation in anticipation of implantation of the mature follicle (Clancy, 2009). Among other hormonal changes, this reduction in estradiol is thought to disrupt the endocrine pathways responsible for ovulation and thus fecundity, leading to an average age at menopause between ~45-55 years across human populations (O'Connor et al., 1998; Thomas et al., 2001; Greenspan and Gardner, 2004; Johnson et al., 2004; Walker and Herndon, 2008). Meanwhile, the human maximum lifespan of ~110 years (Finch, 1990; Ostojić et al., 2009) offers women the chance to live far beyond the age of menopause (Hawkes et al., 2009).

The existence of menopause in humans presents theoretical problems for evolutionary biology and practical problems for medical science. Biologists have long sought to explain the seeming evolutionary contradiction of aging (e.g. Weismann 1889; Medawar, 1952), defined not as the simple accrual of time spent living, but specifically as the senescence of physiological systems with age (Gavrilov and Gavrilova, 2006). Why should selection allow for functional deterioration and the regular occurrence of intrinsic causes of mortality, rather than favoring self-maintenance in perpetuity so long as organisms can avoid extrinsic mortality factors? Reproductive decline, in particular, requires explanation from the standpoint of natural selection (Williams, 1957), since reducing fecundative capacity to zero effectively curtails reproductive success and is of little apparent selective value. Why a large proportion of humans experience the total loss of reproductive function well before the failure of somatic (i.e. non-reproductive) systems remains an open question in the evolutionary study of aging.

In addition to evolutionary issues, and perhaps more immediately relevant to most women, menopause and the postmenopausal lifespan also present significant biomedical challenges. While preservation of somatic physiological integrity often extends beyond the termination of procreative function, hormonal shifts associated with the change in reproductive status may have wide-ranging, deleterious effects on health (Oh et al., 2002; Carr, 2003; Gaspard, 2009). In the United States and other industrialized and industrializing societies, where an increasing proportion of individuals survive well past the age of menopause (Arias, 2010) and populations are skewed toward an older overall average age (Kinsella and Phillips, 2005), enhanced disease risk during the postmenopausal period presents a major public health

dilemma (Mehrotra et al., 2003). On an individual level, quality of life issues and the ability to lead a comfortable life in older age are also socially important (Laditka and Laditka, 2002; Rappange et al., 2010). Critical to dealing with these issues is the development of effective preventive strategies, rather than relying on diagnosis and treatment of already acquired diseases, since the former can reduce the costs of medical care, and just as importantly can avert pain and suffering (Goetzel, 2009; Rappange et al., 2010).

What follows is an attempt to merge the evolutionary and biomedical perspectives on menopause, and to use a comparative and evolutionary framework to inform the study of the postmenopausal lifespan and its medical implications. The range of potentially relevant questions in this field is broad, but the subsequent discussion focuses on an investigation of the specific relationship of exercise and metabolic function in postmenopausal women. Menopause-associated changes in metabolism, body composition, and the musculoskeletal response to exercise, are thought to underlie risk for the development of metabolic and cardiovascular disease. Extrapolating from evolutionary hypotheses for the origin of the postmenopausal lifespan, this study compares the effects of long-term and short-term exercise on the maintenance of resting energy expenditure (REE) and body composition in postmenopausal women. The study tests the hypothesis that high levels of exercise promote the maintenance of basic metabolic function, even in the face of hormonal changes associated with menopause.

Though this study addresses only a very small corner of the vast universe of issues in the study of human menopause, its underlying framework, evolutionary medicine, is broadly applicable to studies in gerontology and reproductive biology.

Evolutionary medicine follows from the principle that modern human health and disease are products of the evolutionary forces that have shaped modern human biology and variation. Hypotheses for the evolution of human physiology and life history offer testable predictions that, upon investigation, can provide a better understanding of the health implications of interactions between genes, environment and behavior, and may lead to better preventive solutions for disease (Eaton et al., 2002). Although the application of evolutionary principles to medical problems is not novel (e.g. Williams and Nesse, 1991; Nesse and Williams 1994), the relatively short formal history of this approach means that little such work deals with menopause (e.g. Sievert, 2006; Trevathan, 2007; Trevathan et al., 2008).

The present study thus represents an expansion of the manner in which postmenopausal physiology, health, and disease are understood, and pertains to the following overarching question: have decreased mortality and increased sedentism in industrialized society combined to produce a situation where a large proportion of women live past menopause, but frequently at great health risk due to deviation from our evolutionary trajectory in the form of too little exercise? Given that many aspects of human physiology and life history evolved under a foraging subsistence regime, where obtaining food required high levels of physical activity, the present research examines the role of regular exercise in shaping the maintenance of metabolic physiological function during the postmenopausal life history period. The narrow research project that forms the main focus of this discussion is detailed below. Before that, however, the project's theoretical framework requires the placement of human menopause in its comparative biological and evolutionary contexts.

CHAPTER 2: COMPARATIVE AND EVOLUTIONARY CONTEXT OF THE HUMAN POSTMENOPAUSAL LIFESPAN

Any semelgametogenic female can theoretically experience menopause and the loss of fecundity if she lives long enough to outlast her supply of oocytes. It should come as no surprise, then, that humans are not unique among mammals in the fact of menopause: documented cases of post-reproductive survival exist in a wide array of captive and wild mammalian species (Cohen, 2004). With the exception of perhaps a handful of matrilineal toothed whale species (Kasuya and Marsh, 1984; Marsh and Kasuya, 1984; Marsh and Kasuya, 1986; Olesiuk et al., 1990; Bloch et al., 1993; Martin and Rothery, 1993; McAuliffe and Whitehead, 2005; Foote, 2008), however, the majority of mammals, including nonhuman primates, exhibit very low rates of female survival to reproductive cessation, with extremely limited post-reproductive longevity (Caro et al., 1995; Packer et al., 1998; Pavelka and Fedigan, 1999; Bronikowski et al., 2002; Bellino and Wise, 2003; Cohen, 2004; Fedigan and Pavelka, 2006). Humans, therefore, stand alone among mammals in the sizable proportion of females that reach menopause, and the considerable length of time by which they live past it.

The uniqueness of the human pattern is especially evident in comparison to the panins (common chimpanzees, *Pan troglodytes*, and bonobos, *P. paniscus*), the taxon with which we share our most recent common ancestor (Goodman et al., 1998). Examination of the physiological basis for menopause in humans and panins suggests that we share a common, possibly ancestral timing of reproductive decline and menopause. On the other hand, comparative data indicate that humans, or at the very least extant human populations, exhibit what is likely a derived pattern of

postmenopausal survivorship and longevity. As such, human life past menopause may be an evolved, species-typical life history stage, achieved via extension of somatic maintenance beyond the termination of reproductive function. As there is a vast literature on the biology of aging (e.g. Medvedev, 1990; Gavrilov and Gavrilova, 2006), what follows is a condensed summary of the relevant evidence and hypotheses, providing a general evolutionary framework for the biomedical study of postmenopausal physiology.

The Timing of Menopause in Humans and Panins

In humans, the age at menopause is often defined as 12-months past the last menses, and is most frequently assessed through recall questionnaires. Although the recall method has some potential for inaccuracy (see Sievert, 2005), it has nonetheless allowed researchers to conduct large-scale studies of the age at menopause in widely dispersed contemporary populations. The data from these different societies are remarkably consistent, with population-average ages at menopause falling largely within the narrow age range of 47-53 years (see Figure 2.1, and see Table A.1 for data and sources). The amount of variation within populations, however, greatly exceeds the between-population range, with individual ages at menopause occurring anywhere between 40-60 years old (Treloar, 1981; te Velde and Pearson, 2002). Understanding the mechanisms underlying this variability is important for interpreting patterns of postmenopausal survival and longevity among humans, as well as for comparison with panins (see below), but the causes of variation in menopausal age remain largely unknown.

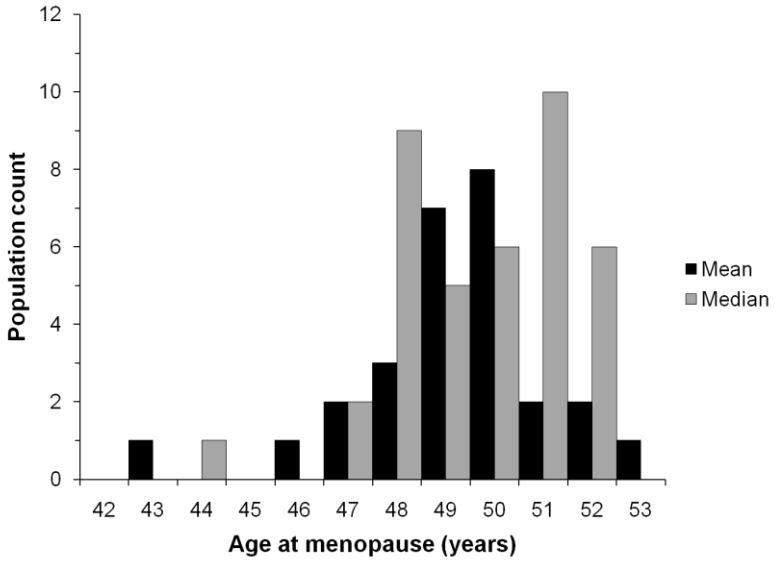

Figure 2.1: Distribution of population-average ages at menopause

Notes: Number of populations (total N=53) with average (mean and median) ages at natural menopause within each age range. See Table A.1 for data and sources.

The genetic basis for menopause, for example, is incompletely understood (Voorhuis et al., 2010), despite extensive research on the genetics of aging more generally (e.g. Finch, 1990; Finch and Kirkwood, 2000). Heritability estimates for age at menopause range from ~30-85% (Torgerson et al., 1997a,b; Snieder et al., 1998; Peccei, 1999; de Bruin et al., 2001; van Asselt et al., 2004; Murabito et al., 2005), demonstrating that genes play some role in the onset of reproductive cessation, but providing little clarity on the relative contributions of genes vs. environmental effects, or the manner in which gene/environment interactions affect the timing of menopause (Vitzthum, 2003; Voorhuis et al., 2010). Linkage analysis, candidate gene association, and genome-wide association studies have only recently begun to identify a few of the many genes probably influencing the age at menopause (Voorhuis et al., 2010).

The importance of behavioral, environmental, and developmental factors are only somewhat better-known than the effects of genes. Cigarette smoking, for example, associates with an earlier age at menopause (see Zenzes, 2000; Mishra et al., 2010). Conversely, a later onset of menopause tends to occur in women who experience fewer lifetime menstrual cycles, either through higher fertility or longer or more irregular cycling patterns (Soberon et al, 1966; Kaufert et al., 1987; Stanford et al., 1987; Whelan et al., 1990; Dahlgren et al., 1992; Torgerson et al., 1994; Cramer et al., 1995; van Noord et al., 1997). Less well-understood are socioeconomic and nutritional effects. Although several studies report correlations between age at menopause and socioeconomic indicators in adulthood (e.g. education, income) and during development (e.g. birth weight, post-natal growth rates), the aggregate results fail to point to consistent relationships, likely due to an abundance of uncontrolled confounders (Flint, 1974; Beall, 1983; Walker et al., 1984; Kaufert et al., 1987; Weinberg et al., 1989; Okofonua et al., 1990; Torgerson et al., 1994; Garrido-Latorre et al., 1996; Cresswell et al., 1997; Gonzalez et al., 1997; van Noord et al., 1997; Chim et al., 2002; Hardy and Kuh, 2002, 2005; Reynolds and Obermeyer, 2003; Ku et al., 2004; Mohammad et al., 2004; Castelo-Branco et al., 2005; Kriplani and Banerjee, 2005; Mishra et al., 2007; Tom et al., 2010; Sloboda et al., 2011).

Achieving a better understanding of the variables involved in determining the timing of menopause clearly requires much additional research, but gaining such an understanding is critical to resolving a disjunction between the medical and evolutionary views of variation in the age at menopause. While medicine tends to pathologize deviation from norms in the age at menopause (Meyer, 2001), the evolutionary perspective instead views such variation as potentially adaptive (e.g.

Gluckman and Beedle, 2007; Ellison, 2010). If variation in the age at menopause correlates consistently with variation in environmental conditions or other life history traits, it may mean that the timing of menopause depends to some extent upon individual life experiences. This fits with the "predictive adaptive response" concept (e.g. Gluckman et al., 2005; Gluckman and Beedle, 2007), which suggests that intraspecific variation in life history traits reflects an evolved flexibility that tailors individual phenotypic expression in response to environmental cues. Expression of life history traits is thus geared towards population-specific maximization of individual lifetime fertility in the face of a varying, yet predictable environment. Since this concept has proven effective in explaining variation in other human reproductive characteristics (e.g. Vitzthum, 2008, 2009), it is likely also applicable to menopause. In this vein, Ellison (2010:16) suggests that:

> …although the biology of reproductive aging may be common to all human populations, the reality of reproductive aging may differ between individuals and populations depending on the ecological conditions under which they live. Phenotypic heterogeneity in gonadal function is associated with ecological conditions for adaptive reasons, and because environments differ, so will patterns of reproductive aging.

If the age at menopause indeed varies predictably with other internal and external factors, this may suggest that the timing of menopause is not only important as the end of reproduction, but also in determining when the post-reproductive period *begins*. This would fit with the idea that the human postmenopausal life history period has evolved due to its positive effects on lifetime selective fitness, as various hypotheses propose, and predicts that postmenopausal physiological maintenance

has been subject to the effects of selection. Pursuing this line of thought has the potential to illuminate factors underlying postmenopausal physiological function and disease.

To understand variation in human reproductive aging from an evolutionary perspective, it is also crucial to investigate the reproductive biology of our closest living phylogenetic relatives, the panins. In chimpanzees and bonobos, evidence for age-related reproductive decline, and by proxy menopause, comes from observations of hormone cycling patterns, sexual swellings and menstruation, examinations of ovarian histology and follicle counts, as well as age-specific fertility patterns. Given that the combined samples of panin studies include widely dispersed populations living under very different conditions (e.g. captive vs. wild), there is considerable variation in the results. Generally, though, the data confirm that panins share with humans an age at menopause between 40-60 years old (Walker and Herndon, 2008), with limited potential for postmenopausal survival (Videan et al., 2006; Atsalis and Videan 2009a,b; Herndon and Lacreuse, 2009).

The bulk of information comes from research on captive common chimpanzees, with a small sample of captive bonobos also having been studied (Gould et al., 1981; Jurke et al., 2000): both species exhibit similar reductions in fecundity and fertility with age. The regularity and frequency of menstrual cycles and the duration of maximal tumescence of sexual swellings all decline gradually with age from peaks during the third decade of life (Graham, 1979; Gould et al., 1981; Jurke et al., 2000; Videan et al., 2006; Lacreuse et al., 2008). During the mid-30s to age 50, reproductive hormone profiles in both panin species begin to resemble those of peri-menopausal humans (Gould et al., 1981; Jurke et al., 2000; Videan et al., 2006), and

ovarian histopathology in aged panins is consistent with the human ovary after menopause (Gould et al., 1981; Videan et al., 2008). Although different chimpanzee populations vary in terms of cycling characteristics and their age-related changes (similar to humans: see den Tonkelaar et al., 1998; Vitzthum, 2009), across populations both menstrual cycling and swellings cease by the late-40s to mid-50s (Videan et al., 2006; Lacreuse et al., 2008).

Although the age-related deline in cycling among panins appears more gradual and drawn out than the average human pattern (te Velde and Pearson, 2002), the rate of ovarian follicle depletion from birth to age 45 is nearly identical in humans and chimpanzees (Jones et al., 2007). Assuming both species share the same "dose-response" threshold of oocytes required for the stimulation of ovulation, this finding suggests a common menopausal age. Jones et al. (2007) also found a constant acceleration of follicle loss in both species, which along with other studies (Leidy et al., 1998; Hansen et al., 2008) contradicts the proposal that the more rapid decline in cycling frequency and regularity in humans is the result of a foreshortening of reproduction relative to the ancestral condition (e.g. Faddy et al., 1992; Cant and Johnstone, 2008). Instead, the weight of the evidence supports the position that, generally, the human and panin age at menopause probably represents a shared, ancestral trait.

Consistent with a common end to ovulation, panin fertility likewise drops off at roughly the same age as in humans. Despite individual potential for childbearing into the late 40s (Puschmann and Federer (2008), captive chimpanzees on average experience a substantial decrease in fertility past age 35 (Graham, 1979) with a corresponding increase in the proportion of pregnancies that terminate in stillbirth or

spontaneous abortion (Roof et al., 2005; Atsalis and Videan, 2009b). In wild chimpanzees, fertility drops precipitously after age 40-44, though a small fraction of females continue to reproduce into the 50-55-year age range (Emery Thompson et al., 2007). Akin to cycling and swelling frequencies, there appear to be population-level differences in fertility termination (Boesch and Boesch-Achermann, 2000; Emery-Thompson et al., 2007), and it is possible that these differences coincide with variation in ecological factors. As in humans, however, these relationships remain largely undetermined (Atsalis and Videan, 2009a,b; Herndon and Lacreuse, 2009).

Postmenopausal Survival and Longevity

In theory, the common age at menopause offers humans and panins similar opportunities for postmenopausal survival, provided similar age-specific mortality profiles. In reality, women survive to menopause at much higher rates and live beyond it for much longer on average than do panins. The conditions of postmenopausal survival and longevity in humans suggest that this pattern is not a byproduct of recent technological developments, but has instead evolved via an extension of somatic maintenance. In this view, a long, healthy postmenopausal lifespan is a species-typical life history trait in humans, and forms an integral part of the overall physiological adaptive suite of menopause.

Although previous researchers (Washburn, 1981; Weiss, 1981; Wood, 1994) have proposed that the postmenopausal lifespan is largely an epiphenomenon of recent secular changes, a great deal of evidence suggests otherwise. During the first half of the 20th century, for example, some populations experienced small secular changes in the age of menopause of ~1.5-2.5 years (Rödström et al., 2003; Nichols

et al., 2006; Danubio and Sanna, 2008; but see Pavelka and Fedigan, 1991), but in the direction of a *later* menopause. Without a concurrent decrease in adult age-specific mortality rates, this would tend to reduce survivorship to menopause and shorten the postmenopausal lifespan, and thus cannot explain the human pattern of postmenopausal survival and longevity.

Industrialized society has certainly seen decreased age-specific mortality and increased survivorship in the recent past, undoubtedly raising the proportion of females living to menopause. Life expectancy (Figure 2.2) and survivorship (Figure 2.3) data for United States females from 1850-2000 show a dramatic increase in average life expectancy at birth and in survivorship from birth to age 45 (a proxy for menopausal age), driven mainly by reduced infant mortality (Gray, 1976). Meanwhile, adult mortality decreased more modestly over the same period, as reflected in conditional survival from age 15 to age 45 (the proportion of women surviving to sexual maturity that also reach menopause) and in life expectancy at age 45. Particularly noteworthy is that in 1850, prior to major improvements in sanitation and medical practice (Cutler and Miller, 2005), ~70% of 15 year olds could expect to live to menopause plus an average of another ~25 years. Thus, any secular trend in postmenopausal survival during the 20th century appears to be simply an expansion of what was already a quite common life history experience, even under the conditions of life in 1850.

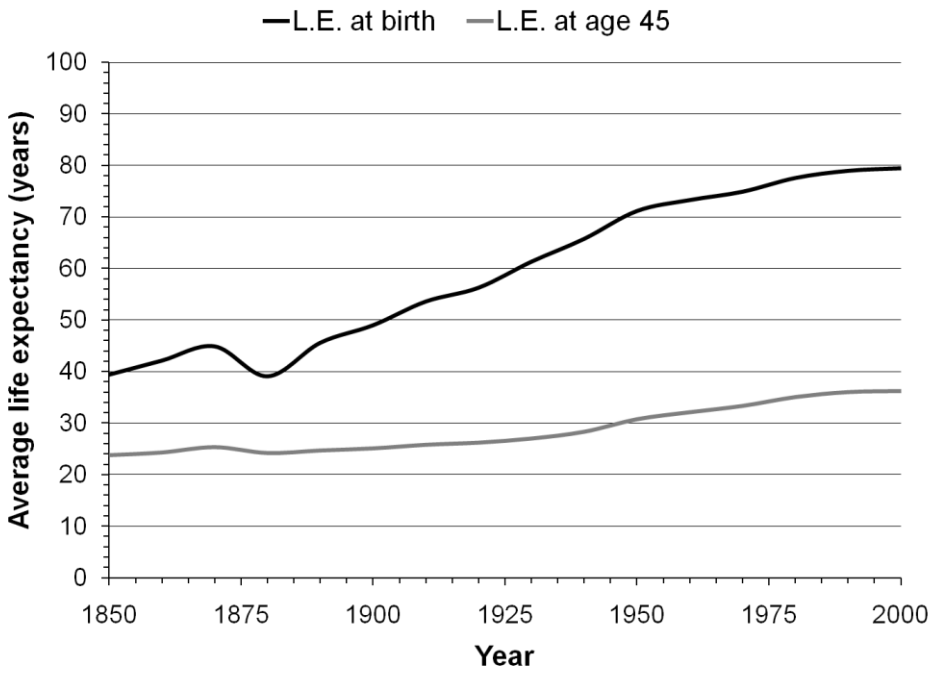

Figure 2.2: Life expectancy in the United States, 1850-2000

Notes: L.E. = Life expectancy, or average years of life remaining at the age in question. Life table data for 1850-1890: Haines (1994); for 1900-2000: Bell and Miller (2005).

While the 19th century United States offers an example of postmenopausal survivorship prior to the secular changes of the 20th century, a better test comes from data on extant hunter-gatherer groups. Despite immense diversity (Kelly, 1995), hunter-gatherer societies share general characteristics that make them good models for mortality and survivorship in non-industrial, non-agricultural people. Hunter-gatherers obtain the bulk of their food from seasonally fluctuating wild plant and animal supplies, practice natural fertility, and lack reliable access to developments that have increased life expectancy in industrialized societies (Wood, 1994; Panter-Brick, 2001; Blurton Jones et al., 2002; Gurven and Kaplan, 2007). Unsurprisingly, a compilation of demographic data on five hunter-gatherer groups (Gurven and Kaplan,

2007; sexes combined, N=2728) shows a pattern of survivorship and life expectancy quite different from the contemporary United States (see Table 2.1 and Figure 2.4). Strikingly, however, the hunter-gatherers resemble the pre-industrial United States in that roughly two-thirds of individuals that reach age 15 also live to age 45, and survive thereafter for an average of another two decades.

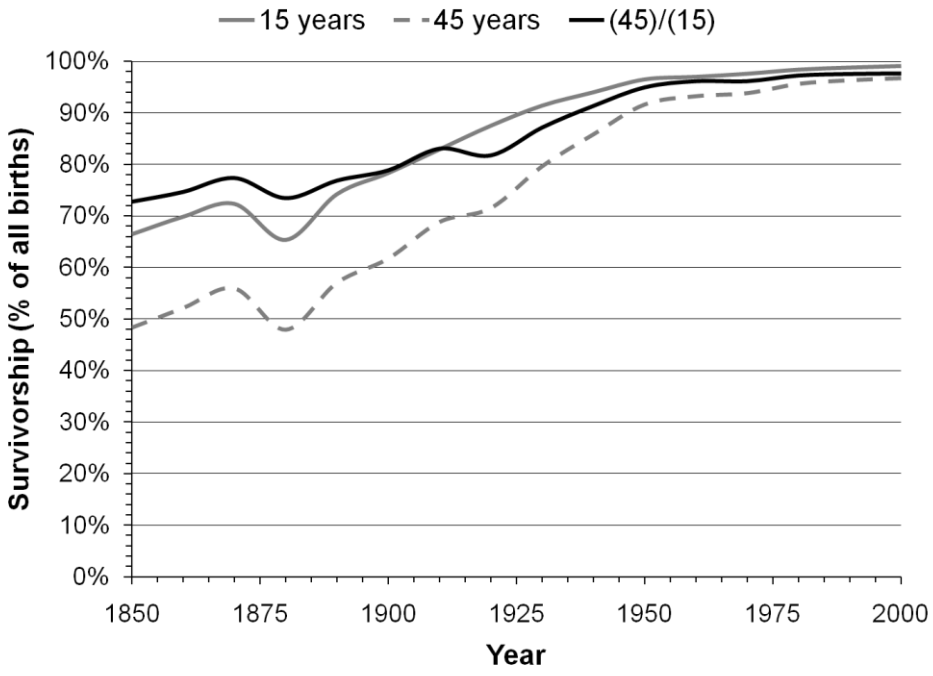

Figure 2.3: Survivorship in the United States, 1850-2000

Notes: Survivorship from birth to age 15 years (solid gray line) and birth to age 45 years (dashed gray line); conditional survivorship from 15-45 years (black line: rate at which individuals who survived to age 15 also survived to age 45). Life table data for 1850-1890: Haines (1994); for 1900-2000: Bell and Miller (2005).

Table 2.1: Life table variables for the United States, hunter-gatherers and panins

	Homo sapiens								*Pan troglodytes*	
	United States		Hadza	Ache	Hiwi	!Kung	Agta	Avg. H-G	Wild	Captive
	1850	2000								
e_0	38	77	34	37	27	36	21	34	13	26
e_{45}	23.2	34.1	24.2	21.1	17.9	19.7	13.7	20.7	5.0	7.2
l_{15}	0.65	0.99	0.57	0.66	0.53	0.59	0.45	0.57	0.37	0.64
l_{45}	0.47	0.95	0.40	0.43	0.29	0.39	0.26	0.36	0.03	0.20
$(l_{45})/(l_{15})$	0.72	0.96	0.70	0.65	0.55	0.66	0.58	0.63	0.08	0.31
PM/LS ratio	0.34	0.43	0.35	0.32	0.28	0.30	0.23	0.32	0.10	0.14

e_0=average life expectancy at birth; e_{45}=average remaining life expectancy at age 45; l_{15}=survivorship to age 15 as fraction of all births; l_{45}=survivorship to age 45 as fraction of all births; $(l_{45})/(l_{15})$=conditional survivorship to age 45 as fraction of all individuals surviving to age 15. PM/LS ratio=average postmenopausal lifespan (PM) as a percentage of average total lifespan (LS) upon reaching 45 years old, calculated as $e_{45}/(e_{45}+45)$. Parameters are for males and females combined.

US data for 1850 from Haines (1994); for 2000 from Bell and Miller (2005). Hunter-gatherer (H-G) and *Pan troglodytes* data from Gurven and Kaplan (2007).

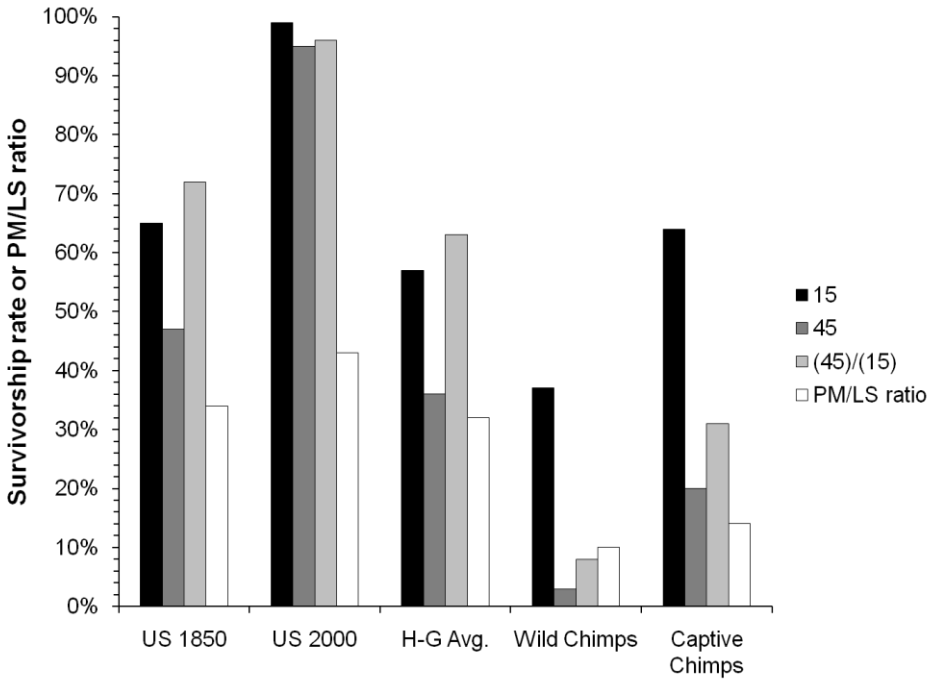

Figure 2.4: Survivorship in the United States, hunter-gatherers and panins

Notes: Survivorship from birth to age 15 years (black bars: l_{15}) and birth to age 45 years (dark gray bars: l_{45}); conditional survivorship from 15-45 years (light gray bars: $(l_{45})/(l_{15})$); and PM/LS ratio=average postmenopausal lifespan (PM) as a percentage of average total lifespan (LS) upon reaching 45 years old, calculated as $e_{45}/(e_{45}+45)$. See Table 2.1 notes for sources.

Also included in Table 2.1 and Figure 2.4 are data on chimpanzee mortality and survivorship (compiled in Gurven and Kaplan, 2007; sexes combined), demonstrating the considerable gap between humans and even captive chimpanzees in the rate and length of postmenopausal survival. Reductions in extrinsic mortality risk provide captive chimpanzees with survival benefits over their wild counterparts, particularly to age 15, but captive chimpanzees do not survive to menopausal age at anywhere near the rates of people in hunter-gatherer societies or the pre-industrial United States. In the wild, on average only 5% of female chimpanzees survive from birth to age 45-50 (Hill et al., 2001; Emery Thompson et al., 2007). Even among

those living to sexual maturity, less than 10% survive to age 45, and those that do reach 45 have at that point completed on average 90% of their total lifespan (Gurven and Kaplan, 2007). There is considerable variation between sites (Hill et al., 2001; Emery Thompson et al., 2007), however, and anecdotal evidence suggests the survival of two wild females for at least 10 years past menopause at Ngogo, in Uganda (Monica Wakefield, personal communication, April 4, 2011), demonstrating the capacity for substantial post-reproductive life in individual wild chimpanzees. Nevertheless, the paired rates of fertility decline and adult mortality in wild and captive chimps suggest that on average, menopause occurs in a very small proportion of all females born, and then only very late in life (Lacreuse et al., 2008; Herndon and Lacreuse, 2009).

Postmenopausal Longevity and the Extension of Somatic Maintenance

Taken together, the data on age-specific patterns of ovulation, fertility, and mortality suggest that while humans and panins share a common timing of menopause, the regular appearance of a long postmenopausal lifespan is unique to humans. In terms of physiological systems, the lifespan of the reproductive apparatus is common to both humans and panins, while somatic systems appear to be maintained for much longer in the former than in the latter. In other words, when it comes to somatic physiological maintenance, panins age faster than humans. The fact that even captive chimpanzees rarely achieve postmenopausal status and then survive only briefly underscores this point, suggesting that despite minimal extrinsic mortality risk in captivity, adult chimpanzees succumb to intrinsic causes of death at higher age-specific rates than do humans (Hill et al., 2001). While adult mortality

increases at roughly the same exponential rate in both chimpanzees and hunter-gatherers, the onset of this rise in intrinsic mortality begins ≥10 years earlier in chimpanzees (Gurven and Kaplan, 2007).

The fact that humans and panins differ for somatic longevity is quite clear, but the physiological mechanisms responsible for maintaining that difference, as well as why we diverged in the first place, are less well-known. There is only limited direct evidence, for example, that chimpanzees experience a higher incidence of specific pathologies at younger ages than humans generally do (Finch and Stanford, 2004; Finch, 2010). Wild chimpanzees show signs of somatic aging beginning in their mid-30s, but these outward signs of deterioration are not always correlated with incapacitation (see Tarou et al., 2002; Finch and Stanford, 2004).

Some physiological correlates of lifespan and somatic maintenance provide potential inroads for comparing the processes of somatic aging in humans and panins, but as yet the relevant data are quite preliminary. One potential area of differentiation is in limiting the oxidative damage done to tissues by the free radical byproducts of oxidative phosphorylation, one of the major causes of aging (Harman, 1956; Matsuo et al., 1993; Sohal and Orr, 1995; Sohal and Weindruch, 1996). Such damage may be prevented by lower production of free radicals via decreased metabolic rate (e.g. Loft et al., 1995; but see Ku and Sohal, 1993; Barja et al., 1994), or by the activity of anti-oxidant free radical scavengers (Sohal et al., 1990, 1993, 1994, 1995; Ku et al., 1993). Humans do have lower mass-specific basal metabolic rate than chimpanzees, even after accounting for allometry (Froehle and Schoeninger, 2006), but direct comparisons of free radical production do not exist. Primates in general have high levels of the anti-oxidant uric acid (relative to other

mammals), but humans and apes share a mutation that elevates uric acid levels above even the primate norm (Ames, 1981; Wu et al., 1992; Friedman et al., 1995; Oda et al., 2002). This fits with apes having the longest lifespans among primates even after controlling for body and brain size (Harvey and Clutton-Brock, 1985; Judge and Carey, 2000). Humans and great apes also share genes for superoxide dismutase anti-oxidants (Fukuhara et al., 2002), the activity of which correlates positively with lifespan across primates, with humans exhibiting the highest relative values (Tolmasoff et al., 1980).

Telomeres protect coding regions of chromosomes during mitotic replication, and shorten with repeated mitotic events until they are of insufficient length to effectively protect DNA (Demerath et al., 2004; Eisenberg, 2011). Thus, telomere length, and the activity of telomerase reverse transcriptase which lengthens telomeres, may provide information about the lifespan of cell lines and species-specific rates of aging (Nakamura et al., 1997; Demerath et al., 2004; Campisi, 2001, 2005). Telomere length appears to be largely conserved in the human/great ape clade (Henderson, 1995; Steinert et al., 2002; Davis and Kipling, 2005). Though an earlier study suggested that humans had especially short telomeres compared to other apes (Kakuo et al., 1999), the validity of that particular comparison has been questioned (Gagneux and Varki, 2001). A caveat of such studies is that telomere length and lifespan are not necessarily correlated across species, as demonstrated by the relatively long telomeres of short-lived rodents in comparison to much longer life but shorter telomeres in humans (Campisi, 2001). Data on telomerase activity in ape somatic cells are non-existent (Davis and Kipling, 2005), but humans and

Japanese macaques (*Macaca fuscata*) exhibit similar tissue-specific patterns of telomerase activity (Gardner et al., 2007).

Finally, the accumulation of errors in DNA translation, transcription and macromolecular synthesis, and reduced energy allocation to maintenance with age also lead to physiological senescence (the "error catastrophe", or "disposable soma" theories: Orgel, 1963, 1970; Harrison and Holliday, 1967; Lewis and Holliday, 1970; Holliday and Tarrant, 1972; Kirkwood 1977, 1980; Kirkwood and Holliday, 1979; Martinez, 1996). In primates very little research addresses these issues, though the results are consistent with theoretical expectations. A single study (Cortopassi and Wang, 1996) found that humans have a higher rate of DNA repair than does the shorter-lived gorilla (*Gorilla gorilla* ssp.). Overall, the data point to the presence of physiological mechanisms for lifespan extension in humans, but not necessarily to the exclusion of apes. Clearly, much work remains to be done in order to establish the proximate mechanisms by which the human lifespan exceeds that of our closest primate relatives.

Various hypotheses also seek to explain the ultimate, evolutionary processes by which human postmenopausal longevity has arisen, in particular because a long post-reproductive life history period contradicts traditional theory on the relationship between natural selection, aging and lifespan (e.g. Medawar, 1952; Williams, 1957; Hamilton, 1966; Kirkwood, 1977, 1980; Kirkwood and Holliday, 1979; Charlesworth, 1994). According to evolutionary aging theory, selection favors somatic maintenance only as long as required to ensure the "…necessary immortality of the germline…" (Kirkwood and Shanley, 2010:24), the precise timing of which depends upon environment-specific extrinsic mortality risk and species-specific fertility rates. At

ages when most members of a birth cohort have succumbed to extrinsic causes of mortality, those still living retain very little reproductive potential relative to the total fertility of the entire birth cohort; selective pressure for continued somatic maintenance diminishes beyond that point, and the rate of intrinsic mortality correspondingly rises rapidly. From this perspective, postmenopausal women retain no reproductive value, and the rate of human postmenopausal survival and longevity is thus quite paradoxical (Hamilton, 1966).

The human exception to these theoretical expectations may stem from another trait that, among primates, humans express uniquely: namely, food sharing (e.g. Hamilton, 1966:36. refers to "…altruistic contributions due to post-reproductives…"). Humans represent an extreme example of the general primate pattern of slow development and high offspring investment, meaning that the "necessarily immortal" human germline is passed on to energy-needy young that remain nutritionally-dependent for far longer than other primates. Humans also reproduce more quickly than other primates, so that they have multiple dependent young simultaneously. As such, raising human children so they can pass on the germline requires an immense quantity of daily calories (Gurven and Walker, 2006). To support this energy-intensive reproductive pattern, humans share food more often, in larger quantities, and across a broader range of dyadic relationships than any other primate (Hrdy, 2009). In terms of the evolution of longevity, this means that by sharing food in support of younger relatives' reproduction, older adults could boost inclusive fitness and thereby enhance their age-specific reproductive value (Kaplan et al., 2000; Carey and Judge, 2001). This creates a feedback loop between selection for extended somatic maintenance and decreased adult morality at increasingly older

ages (Carey and Judge, 2001). Recent models show that human mortality patterns in non-industrialized societies are consistent with lifespan extension due to the inclusive fitness effects of intergenerational food sharing (Lee, 2003, 2008).

Providing for offspring plays a prominent role in hypotheses for the evolution of human longevity through effects on selective fitness. Male-centered evolutionary hypotheses for human longevity (Kaplan et al., 2000; Marlowe, 2000; Tuljapurkar et al., 2007) rely on the idea that procuring and sharing high-quality food items are the primary route via which older men attract younger women. This allows men to take advantage of their iterogametogenesis and to continue reproducing (and thus retain reproductive value) after female members of their own birth cohort reach menopause, thereby selecting for male lifespan extension.

Specific to females, the “Mother Hypothesis” (Williams, 1957; Hamilton, 1966; Peccei 1995a,b, 2001a,b; 2005) and “Grandmother Hypothesis” (e.g. Hawkes et al., 1989; 1997; 1998; O’Connell et al., 1999; Hawkes 2003; Blurton Jones et al., 2005) both propose that the postmenopausal lifespan evolved because it allowed women to boost lifetime reproductive success. In the former, postmenopausal mothers benefit directly by eschewing risky new pregnancies that could jeopardize the survival of existing dependent offspring. In the latter, postmenopausal women indirectly increase fitness by sharing food to promote grandchild production and survival. Various studies show data from extant populations or from mathematical models to be consistent with these hypotheses’ predictions (Mayer 1981, 1982; Turke, 1988; Sear et al., 2000, 2002; Shanley and Kirkwood, 2001; Voland and Beise, 2002; Sousa, 2003; Lahdenperä et al., 2004; Shanley et al., 2007; Fox et al., 2010; but see

Hill and Hurtado, 1991; Jamison et al., 2002; Madrigal et al., 2005; Lahdenperä et al., 2010; Kachel et al., 2011).

While many of the specific tenets of the male- and female-centered hypotheses differ, they all share one crucial argument. In all cases, active foraging and food sharing in support of offspring production and viability are proposed to have imbued humans with the potential for reproductive value at much older ages than expected from theory, or from comparative data on panins. By extension, these hypotheses predict that selection has favored human phenotypes that retain the capacity for somatic maintenance at those older ages. As such, the human postmenopausal period is interpreted as an evolved, species-typical life history stage, as integral to the human life course as adolescence or childhood, and characterized by low rates of intrinsic senescence in physiological systems, at least into the seventh decade of life (Gurven and Kaplan, 2007).

This life-history interpretation informs the study of menopause and the postmenopausal lifespan from the perspective of evolutionary medicine. Following the reasoning behind the evolutionary hypotheses, we can draw inferences about human physiology that are relevant to understanding extant health issues. For example, we might expect that the evolutionary extension of somatic maintenance should foster low rates of chronic and degenerative diseases, and overall good health during the postmenopausal life history period, at least through the sixth and into the seventh decades of life. In addition, given the role of foraging in gaining later-life fitness benefits, we might predict a role for exercise in postmenopausal somatic maintenance. As discussed below, however, these expectations are not always met and the discrepancies merit further study.

CHAPTER 3: MENOPAUSE AND MAINTENANCE OF METABOLIC PHYSIOLOGY

Contrary to evolutionary expectations of low mortality and high somatic integrity in the early postmenopausal period, mid-life for women in industrialized society represents a period of increasing disease risk. This is particularly true with regard to the "metabolic syndrome", the combination of obesity and insulin resistance that increases risk for cardiovascular disease and type 2 diabetes, although other aspects of postmenopausal health are no doubt important and perhaps also related to metabolic function (e.g. osteoporosis: Stini, 1995; Choi and Pai, 2003; cognitive function: Herndon, 2010). Declining metabolic health in women across the postmenopausal period relates to reductions in resting energy expenditure (REE), changes in body composition including increased fat mass and reduced skeletal muscle, decreased physical activity, and lower levels of the reproductive hormone estradiol-17*ß* (Astrup, 1999; Bosy-Westphal et al., 2003; Carr, 2003; Hunter et al., 2004; Qiao et al., 2008; Lovejoy and Sainsbury, 2009; Enns and Tiidus, 2010). The association between postmenopausal life and disease is so extensive that the medical community often views menopause itself as a condition of hormone deficiency requiring treatment, rather than a natural transition between life history periods (Meyer, 2001).

Given disease risk figures in the United States (from the years 2005-2008), it is not hard to see why this view prevails: among women aged 45-64, 40% are obese, 41% are hypertensive, and 14% are diabetic; in women aged 20-44 these rates are, respectively, 33%, 8% and 4% (data source: National Health and Nutrition Examination Survey, obtained from National Center for Health Statistics, Health Data Interactive, http://www.cdc.gov/nchs/hdi.htm, accessed on February 10, 2011). Of

new type 2 diabetes diagnoses in adults over age 20, 55% occur during the 45-64 year age range, with an additional 20% coming after age 65 (Centers for Disease Control and Prevention, 2011). Rather than supporting the evolutionary view, these numbers instead lend credence to the idea that the postmenopausal lifespan is a byproduct of recent reductions in adult mortality via secular means: as an "unnatural" extension of life, the postmenopausal period represents a state of "…uncontrolled degenerative loss of homeostasis…" (Austad, 1997:166).

In contrast to the above view, however, hunter-gatherers without access to medical care appear not to experience the high rate of decline in early postmenopausal somatic maintenance seen in industrialized populations. Degenerative diseases in foraging populations (as far as they can be diagnosed) are extremely rare, accounting for less than 3% of deaths before age 60 (in the Ache and !Kung: Howell, 1979; Hill and Hurtado, 1996; Gurven and Kaplan, 2007). Although degenerative diseases become more common as the causes of death after age 60 (rising to ~20% and ~40% in the aforementioned groups, respectively), obesity, hypertension, heart attack and stroke are extremely rare (Eaton et al., 1988; Gurven and Kaplan, 2007). Anthropometric work among the Hadza hunter-gatherers demonstrates that average body fat percentage remains constant at about 19% in women from age 18-75 (Sherry and Marlowe, 2007), in stark contrast to the increase in body fat with age in postmenopausal women from industrialized societies (Heymsfield et al., 1994). Finally, anecdotal and empirical evidence points to the maintenance of physical vigor in old age in foragers (Hawkes et al., 1989; Blurton Jones et al., 2002; Walker and Hill, 2003), including the observation that older Hadza women tend to work longer and perform difficult foraging tasks more frequently than

women of reproductive age (Hawkes et al., 1989, 1997). These data show that the metabolic syndrome is rare among hunter-gatherers, likely related to an absence of age-related body composition change and continued physical activity. Maintenance of somatic physiological systems well past menopause appears to be the hunter-gatherer norm, with an absence of the related high mortality rates that would be present in industrialized society without advanced medical treatment.

In evaluating the potential cause(s) of postmenopausal health differences between women living in industrialized vs. hunter-gatherer societies, it is important to understand the divergent conditions under which they live from a biocultural and evolutionary perspective. One of the most important physiological changes with menopause is the reduction in levels of the steroid hormone estradiol-17β, which is associated with a variety of health risk factors in postmenopausal women (e.g. Torréns et al., 2009; Enns and Tiidus, 2010). This "hyposteroidal" physiological environment is thought to cause disease by undermining the proper functioning of various somatic physiological systems, including those related to metabolic health (thus the prescription of estrogen replacement therapy). This hypothesis, however, is contrary to expectations if the postmenopausal lifespan indeed represents an evolved life history period. According to Austad (1997:166): "…if menopause *is* an adaptive physiological state molded by evolution…then natural selection would presumably have tailored postreproductive physiology to the hyposteroidal state…" [emphasis in the original]. In other words, if selection promoted the extension of somatic maintenance past menopause, then one would expect postmenopausal physiology to retain functional capacity *despite* reduced estradiol-17β levels.

Rather than see this necessarily as a contradiction, it is possible that factors other than just a reduction in steroid hormone levels affect the ability of metabolic systems to maintain their operations after menopause. Given that physiological systems act not in isolation, but interact and affect one another, it seems reasonable that the physiological effects of behavior and experiences during pre-menopausal life could extend into the postmenopausal period. In the same way that it is reasonable to suspect that selection would have molded our species' postmenopausal physiology to operate under hypersteroidal conditions, it is also reasonable to predict that the environment (both internal and external) under which individual metabolic physiological systems develop and operate across the lifespan might then predispose those systems to function better or worse in the hyposteroidal postmenopausal environment. If this is the case, we might then expect the prevailing conditions of hunter-gatherer life (which, in the general sense, have constituted the dominant environment under which human physiology has evolved) to be critically important to preparing metabolic physiological systems for operation in the low-estradiol milieu after menopause. From this perspective, cultural variation in subsistence and reproduction may be particularly important: if postmenopausal physiology initially evolved in foraging populations, then major deviations from that range of conditions across the lifespan may have important consequences for the proper maintenance of physiological systems after menopause.

The experience of women in industrialized countries differs in a variety of ways from women's lives in modern hunter-gatherer societies, and many of these same differences likely distinguish industrialized life from conditions during the evolution of the postmenopausal life history period. For one, Hawkes (2010) has

suggested that decreased infant and childhood mortality may remove a filter (e.g. Forbes, 1997) and promote higher adult disease risk, if phenotypes prone to pre-adult mortality without public health improvements may also be prone to chronic disease (Hawkes, 2010). Second, reproductive history also diverges between women in contraceptive-using, low-fertility industrialized populations, vs. women practicing natural fertility. In the latter, higher birthrates, longer nursing and more frequent lactational amenorrhea (Wood, 1994) mean fewer lifetime ovulatory cycles and lower exposure to estrogens, possibly related to decreased risk for reproductive cancers (Henderson et al., 1985; Eaton et al., 1994; Bernstein, 2002; Yang and Jacobsen, 2008). The same factors, given their relationship to estradiol-17β levels, could also relate to metabolic function in the low-estrogen, postmenopausal physiological environment (Xue and Michels, 2007). Third, diets in industrialized societies, too, differ greatly from the seasonally variable wild plants and animals that constitute hunter-gatherer diets, and disparities in fat content and composition, fiber, and simple carbohydrates are likely related to higher risk for atherosclerosis, obesity, and insulin resistance in industrialized populations (Eaton and Konner, 1985; Eaton et al., 1997; Cordain et al., 2000, 2002; Konner and Eaton, 2010).

The present study focuses on a fourth factor, the substantial difference in physical activity between hunter-gatherer women, who engage in regular, vigorous physical activity to obtain food, and the more sedentary women of industrialized societies (Hayes et al., 2005). Previous work in evolutionary medicine has addressed the topic of low exercise levels in a general sense (Cordain et al., 1997; Eaton and Eaton, 2003; Chakravarthy and Booth, 2004), but it is important to also consider the particular relationship between exercise and menopause. Menopausal hormonal

shifts, for example, put women at additional risk (vs. men) for the changes in body composition and metabolic physiology that signal risk for developing metabolic and cardiovascular diseases (Major et al., 2005; Torréns et al., 2009). It is established that exercise has considerable potential to prevent or possibly reverse these trends, but the manner in which physical activity manifests improvements in metabolic health and the importance of the timing of exercise relative to menopause are less well-understood. While the current medical paradigm surrounding menopause focuses on exercise as a treatment for age- and hormone-related diseases after they have already developed, prevention strategies remain remarkably understudied (Teede et al., 2010). The evolutionary approach to exercise and its effects on postmenopausal physiology has especially high potential for generating preventive methods against the development of metabolic syndrome.

There are several reasons to investigate preventive aspects of physical activity, most notably the determination that exercise interventions to treat metabolic and musculoskeletal deterioration after menopause are not universally effective (Asikainen et al., 2004). In fact, it appears that several aspects of skeletal muscle's metabolic response to exercise may be lost in older people who have become more sedentary with age, but not in people who have maintained higher levels of exercise as they grow older (parameters such as vascularization: Harris, 2005; and the growth hormone/insulin-like growth factor-I axis: Grounds, 2002). These observations form part of the rationale for the previous suggestion (above) that the physiological conditions of pre-menopausal life may shape the manner in which metabolic physiology responds to the hyposteroidal postmenopausal environment. There may be a critical period prior to, or coinciding with, the menopausal hormonal shift, during

which metabolic and musculoskeletal deterioration can be prevented, and after which such capacity may be lost or decreased (Appt and Ethun, 2010). Thus, the evolutionary perspective can play an important role in expanding the manner in which postmenopausal exercise and disease are understood and approached clinically.

To evaluate the effects of physical activity on postmenopausal metabolic physiological function, the present study examines the relationship between age, exercise and resting energy expenditure (REE; also known as basal metabolic rate, or BMR) in postmenopausal women. Measurement of REE proceeds under standardized laboratory conditions: subjects must be awake but restful, 10-12 hours post-absorptive (i.e. fasting) and under thermoneutral conditions (Boothby and Sandiford 1929; Benedict 1938; Ulijaszek 1992; McNab 1997; Hulbert and Else, 2004). As such, REE represents the energy cost of fundamental physiological processes and tissue turnover, accounting for ~70% of daily energy expenditure (depending on physical activity level), and is an indicator of basic metabolic function. Older people tend to have lower REE, partly as a function of changes in body composition (Keys et al., 1973; Fukagawa et al., 1990; Poehlman et al., 1991; Poehlman, 1992; Heymsfield et al., 1995; Pannenmans and Westerterp, 1995; Roberts, 1995; Visser et al., 1995; Klausen et al., 1997; Piers et al., 1998; Henry, 2000; Hunter et al., 2001; Puggaard et al., 2002; Bosy-Westphal et al., 2003; Rothenberg et al., 2003; Krems et al., 2005; Alfonzo-González et al., 2006; Roberts and Rosenberg, 2006). Additionally in women, menopausal reductions in estrogen levels exacerbate the effects of age on REE (Carr, 2003; Lovejoy and Sainsbury, 2009). Low REE correlates with risk for weight gain and obesity, which in turn increase risk for type-2 diabetes and cardiovascular disease (Must et al. 1999).

Counter to the effects of age, physical activity may affect metabolic rate such that more active people tend to have higher REE. While results are mixed (e.g. Westerterp, 1998), the positive correlation between exercise and REE in younger adults is relatively well-established, explained largely by higher fat-free mass in the form of skeletal muscle with increased exercise (Poehlman, 1989; Stiegler and Cunliffe, 2006; Catenacci and Wyatt, 2007). Reductions in fat-free mass and skeletal muscle mass over time may account for the age-related decrease in REE (Bosy-Westphal et al., 2003) and are tied closely to increasingly sedentary behavior and estrogen reductions (Astrup, 1999; Hunter et al., 2004; Enns and Tiidus, 2010).

Reduced physical activity with age may thus link low REE and low hormone levels to increased postmenopausal weight gain and risk for obesity-related diseases, but the effects of exercise on REE in healthy postmenopausal women are surprisingly understudied (Starling, 2001). This is especially important since the relationship between exercise, body composition and REE may differ between people older and younger than the age of ~50 years (Speakman and Westerterp, 2010) and in relation to menopause (Dionne et al., 2004). Given the low levels of activity in industrialized populations (Hayes et al., 2005; but see Westerterp and Speakman, 2008), it is not surprising that most studies of the effects of exercise on REE in postmenopausal women have consisted of exercise interventions in formerly sedentary individuals.

Intervention studies have employed disparate methods and study designs, and thus have produced variable results. Two studies found that six months of endurance or combined endurance and resistance exercise resulted in fat loss and increased aerobic fitness (Santa-Clara et al., 2006) or strength (Thompson et al., 1997). These training regimes failed to change fat-free mass, however, and both

studies actually found significant *decreases* in REE over time with exercise (Santa-Clara et al., 2006), or with exercise and diet (Thompson et al., 1997). Another six-month investigation (Dionne et al., 2004) compared the effects of resistance training in pre- and postmenopausal women, showing that the younger women adapted to exercise by increasing muscular strength, fat-free mass and REE. Postmenopausal women, meanwhile, lost fat with training and made gains in strength and fat-free mass similar to the younger women, but did not experience a change in REE. Fat-free mass did not differ between younger and older women at baseline, but REE did (1379 vs. 1263 kcal/d, respectively), more so after training (1451 vs. 1247 kcal/d).

Shorter training interventions have had more mixed results. Ryan et al. (1995), in a 16-week study, compared resistance training alone to resistance training paired with a weight-loss diet in postmenopausal women. Within groups, neither fat-free mass nor REE increased significantly with training, here again despite gains in muscular strength. When the groups were pooled, however, modest increases in fat-free mass of ~1 kg and in REE of about 50 kcal/d, or 104% of baseline REE, became significant. In contrast, a 15-week resistance training program with high- and low-intensity exercise variants and a non-exercise control group found no changes in REE or body composition with training, aside from a 1 kg decrease in fat mass among the low-intensity sample (Taaffe et al., 1995). Three-quarters of that study's subjects continued in the training program for a full year, but despite the length of their participation, failed to change body composition or REE significantly. As with other studies, the subjects gained muscular strength, and interestingly, the high-intensity training group showed a significant regional increase in upper limb fat-free mass. This did not, however, affect whole body fat-free mass or REE (Taaffe et al. (1995).

Finally, two training interventions studied postmenopausal women alongside older men and reported results only for the pooled samples—thus it is unknown whether the results reflect men's and women's responses to exercise equally. One of these studies consisted of a 26-week resistance training program, resulting in significant increases in fat-free mass and reductions in fat mass and body fat percentage, and a significant increase in REE from 1287 to 1374 kcal/d (Hunter et al., 2000). The second combined male/female study consisted of a 14-week bicycle training program, finding increases in fat-free mass and aerobic fitness, reduced fat mass and body fat percentage, but no change in REE (Morio et al., 1998).

Only one study has investigated the relationship of sustained, habitually high levels of activity to the maintenance of REE in postmenopausal women. Van Pelt et al. (1997) compared REE in pre- and postmenopausal runners and swimmers that were highly trained (competition times 127 ± 2% of age-specific world records) and made a simultaneous comparison between sedentary pre- and postmenopausal women. They found that after adjusting for differences in fat-free mass, postmenopausal sedentary women had significantly lower REE than premenopausal sedentary women (1248 vs. 1368 kcal/d, respectively), but that the premenopausal and postmenopausal athletes did not differ (1368 vs. 1416 kcal/d). Though Van Pelt et al. (1997) did not make a statistical comparison, the postmenopausal athletes' REE was 120 kcal/d, or 10% higher than in their sedentary, age-matched counterparts.

The results of Van Pelt et al. (1997) are compelling and call for attempts at replication, though none currently exist. Thus, the need for additional data merits further study of the effects of regular exercise on postmenopausal REE. In addition, the sample of Van Pelt et al. (1997) is relative narrowly constrained in terms of activity

level, since all of the active subjects were highly trained athletes. It may be useful to determine whether more moderate levels of exercise have the same effects on REE, both in terms of the practicality of clinical exercise prescription and for comparison to the activity levels of hunter-gatherer women, which vary under different ecological conditions (Panter-Brick, 2002). Finally, it is important to compare the influence of long-term habitual activity directly to the effects of short-term training interventions, in order to evaluate their relative potential benefits for metabolic health, and the importance of the timing of exercise in the interest of lowering disease risk. While the magnitude of the habitual-activity effect on REE (10% higher) from Van Pelt et al. (1997) falls within the range of effects of training in some of the intervention studies (7-10% higher), this comparison needs to be made formally within a single study.

The present study examines the relationship between age, body composition, aerobic fitness, physical activity level, and REE in a sample of postmenopausal women recruited from the San Diego, CA area. The main study design compares women with long-term habits of regular exercise to women who were sedentary upon recruitment and then completed a 16-week program of aerobic and resistance training. The data at baseline are also analyzed cross-sectionally across all physical activity levels ranging from sedentary to highly-active. Although the study proceeds from an evolutionary perspective on the role of exercise in shaping postmenopausal metabolic physiology, the three main hypotheses tested here are of interest for the clinical prescription of exercise for prevention and treatment of metabolic and cardiovascular disease. These hypotheses are as follows:

1. Exercise ameliorates the age-related decline in REE. In other words, age-specific REE will be higher in more active women.

2. The association between body composition and exercise, in particular a positive correlation of fat-free mass with physical activity level, explains much of the apparent effect of exercise on age-specific REE.

3. The short-term training intervention will have an effect on REE of a magnitude similar to that of longer-term, habitual activity. This is a working hypothesis derived from the informal comparison of previous studies' results as described above.

For comparative purposes, this study also includes a pilot investigation of foraging activity data for three postmenopausal women from the Hadza hunter-gatherer society. The Hadza live in a highly seasonal, savanna-woodland environment near Lake Eyasi in northern Tanzania, and women mainly forage for baobab fruit and berries, dig for tubers, and collect eggs, small birds, and other foods (Crittenden, 2009). There are very few available data on the physical activity level of women who forage for a living, and those that do exist (i.e. for the Ache and !Kung; Leonard and Robertson, 1992) are pooled data for adult women of all ages. The strenuous nature of postmenopausal women's work among the Hadza is mentioned anecdotally elsewhere (e.g. Hawkes et al., 1989), but without formal activity budgets. The data presented here, though limited, are thus the first empirical estimates of physical activity level specifically in postmenopausal hunter-gatherer women.

CHAPTER 4: METHODS

Subjects

Women were recruited through the San Diego Senior Olympics and the La Jolla YMCA, as well as by posting fliers on UCSD campus and by word of mouth through subjects already in the study. Potential subjects completed a screening interview and a health and physical activity questionnaire. Inclusion in the study required women to be naturally postmenopausal (i.e. non-surgically), defined at screening as one year since last menstruation, and confirmed by assays of serum follicle stimulating hormone (FSH) and estradiol-17β. Women were excluded if they had FSH<30 mIU/ml or estradiol-17β >25 pg/ml (Strauss and Barbieri, 2004). Other exclusion criteria included: smoker, abuser of alcohol/other drugs; hypo- or hyperthyroid (serum TSH <0.3 or >5.5 μU/ml, respectively; Spaulding and Utiger, 1981; Pittas and Lee, 2003); underweight or obese (BMI<18.5 or >30 kg/m2, respectively); weight instability within the past six months (±>5% of body weight); hormone replacement therapy within the past six months (may raise REE: Aubertin-Leheudre et al., 2008); history of metabolic, respiratory or cardiovascular disease, or high blood pressure; or contraindication for maximal aerobic testing as determined by the Physical Activity Readiness Questionnaire (Chisholm et al., 1975; Shephard, 1988; Thomas et al., 1992; Cardinal et al., 1996). Of 50 women that underwent the full screening, 41 met the criteria for inclusion.

Measurement Schedule and General Study Design

After the screening interview, subjects scheduled clinical and laboratory visits for continued testing over 16 weeks, with appointments scheduled for baseline, or

"week 0", and then at 5, 10 and 16 weeks past baseline. The time from screening to baseline measurement was three to four weeks. Baseline procedures (detailed methods for all study measurements are below) included a blood draw for hormone assays and aerobic fitness testing, as well as metabolic and body composition assessments which occurred again at 5, 10 and 16 weeks. A second aerobic fitness test was performed during week 16.

Baseline data for the entire, pooled sample were analyzed cross-sectionally, while measurements from all four testing periods were analyzed longitudinally. Four subjects were dropped from the study for cardiovascular or musculoskeletal reasons prior to participating in the longitudinal portion of the study. The remaining 37 subjects included in the longitudinal study were split into two groups on the basis of exercise habits. Women who exercised ≥5 hours per week, and had been doing so for ≥10 years, were placed into the "Active" group (N=19) and maintained their regular exercise routines throughout the 16-week duration of the study. Sedentary subjects exercising ≤2 hours per week at baseline, and who had never engaged in a program of regular exercise, were placed into the "Training" group (N=18). After baseline measurements, the Training group subjects completed a 16-week exercise training program at the La Jolla YMCA (see details below). All subjects followed the same testing schedule as outlined above and underwent the same measurement regime described below.

Physical Activity Assessment

During the screening interview each subject's normal level of exercise was verbally assessed, asking for information on hours per week and general type(s) of

exercise. There was considerable variation in exercise habits across the sample. To formally assess this variation, subjects were asked to keep activity diaries throughout the study period. Each subject maintained her diary for approximately four weeks prior to testing, and those records were used to derive baseline average daily physical activity level for each individual. Subjects recorded all activities in which they engaged each day that were at least as strenuous as a casual walk, along with details about each activity including duration (in minutes), distance covered, and any additional information on perceived exercise intensity.

Standardized energy intensity coefficients were assigned to each recorded activity (as metabolic equivalent of task, or MET, intensities, from the Compendium of Physical Activities: Ainsworth et al., 2000), using the descriptions accompanying the coefficients to match them as closely as possible to the recorded activities. For each activity, the minutes spent in that activity were multiplied by the corresponding MET coefficient to arrive at a time x intensity value—all such values for each day were then summed. The remaining time each day not spent in activity (total minutes per day minus minutes spent exercising) was multiplied by a MET value of 1.0 and added to the activity sum. The grand total was then divided by 1440 (total minutes in one day) to arrive at daily physical activity level, and all daily values across the four weeks were averaged for each subject.

Resting Energy Expenditure and Body Composition

Resting energy expenditure (REE) and body composition measurements occurred at the UCSD General Clinical Research Center (GCRC) in the morning between 0700 and 0930. Subjects spent the previous night at home, refraining from

physical activity and fasting for 12 hours prior to testing. They were responsible for their own transportation to the facility. Upon arrival, subject height and weight were measured on a stadiometer (Ayrton S100, Prior Lake, MN) and digital scale (Scale-Tronix 5005, White Plains, NY), respectively. This was followed by assessment of REE, which involved measurement of $\dot{V}O_2$ and $\dot{V}CO_2$ using a ventilated-hood, open-circuit respirometry system (VMax Encore VS-29, CareFusion, San Diego, CA). Subjects lay supine on a hospital bed in a thermoneutral, temperature-controlled room (Kashiwazaki et al., 1990), and one-minute average gas volumes were recorded over a period of 25 minutes. To ensure that REE data came from fully relaxed subjects, only the final 10 minutes of gas volumes were used, and were converted to kcal following Weir (1949).

After REE assessment, subjects were provided with breakfast, and then underwent total body bioelectrical impedance analysis with tetrapolar lead arrangement (Quantum II, RJL Systems, Clinton Twp., MI). Resistance and reactance values were entered along with height, weight and age into a proprietary software package (Cyprus 2.7, Body Composition Analysis, RJL Systems) to estimate body fat percentage, fat mass, body cell mass, extracellular mass, total body water, intracellular water, and extracellular water. Anthropometric measurements were also taken, including hip and waist circumferences, and ten skinfold thicknesses using Lange calipers (Beta Technology, Santa Cruz, CA): pectoral, midaxillary, triceps, biceps, subscapular, abdominal, suprailiac, thigh, suprapatellar, and medial calf. One individual (Hau T. Ngo) conducted 83% of the skinfold measurements over the course of the entire study, minimizing the problem of inter-observer error (Lohman et al., 1988). Thickness values were used to calculate body fat percentage using two

different sets of equations (four sites: Durnin and Womersley, 1974; seven sites: Jackson et al., 1980).

Body composition was also assessed by whole body dual-energy x-ray absorptiometry on a Hologic Discovery W scanner (Bedford, MA), but only at the baseline and 16-weeks appointments. Variables estimated from dual-energy x-ray absorptiometry included total tissue area and mass, bone mineral content, bone mineral density, fat and lean mass components, and fat percentage. The software provided total body values for each variable, as well as regional values for each arm and leg, left and right ribs, thoracic and lumbar vertebrae, pelvis, and head.

Maximal Aerobic Capacity

Maximal aerobic capacity ($\dot{V}O_{2MAX}$) testing occurred at the Human Exercise Physiology Laboratory in the UCSD Division of Physiology. Subjects were instructed to refrain from vigorous physical activity and consumption of caffeine for the duration of the day prior to testing. Tests were performed on an electronically-braked cycle ergometer (Quinton Instruments Co., Groningen, Netherlands), and subjects breathed through a two-way breathing valve with a “snorkel-type” mouthpiece while wearing a nose-clip (Hans-Rudolph, Kansas City, MO, USA). Respiratory gas exchange (15-second average) was measured using open-circuit respirometry (TrueMax, ParvoMedics, Salt Lake City, UT, USA). Cardiac rhythm and arterial oxygen saturation were monitored, respectively, via Lead II EKG and pulse oximetry using a forehead sensor (RS-10, Nellcor N-395 Oxismart XLTM, Mallinckrodt, St. Louis, MO, USA; see Yamaya et al., 2002). A project physician supervised and monitored each test for signs of cardiovascular distress.

The testing protocol was slightly modified from standard rates of workload increase (e.g. ACSM, 2006) in younger adults, because older adults tend to lose aerobic capacity with age (Sidney and Shephard, 1977; Jackson et al., 1996; Tanaka et al., 1997; Hollenberg et al., 1998; Patterson et al., 1999; Eskurza et al., 2002). Using a recent review of exercise testing in older adults (Huggett et al., 2005) as a template, the following protocol was followed: subjects warmed up for 5 minutes at a resistance of 25 watts (W); at the 5-minute mark, and at one-minute intervals thereafter, resistance was increased by 15 W. This pattern of increase continued until the subject reached volitional fatigue, at which point the test ended. The gas analyzer was calibrated for air composition and flow volume before each test, and room temperature, humidity and atmospheric pressure were noted so that gas volumes could be converted to STPD. The analyzer recorded 15-second average F_EO_2, F_ECO_2, and $\dot{V}_E$ (L/min), which were used to calculate $\dot{V}O_2$. The mean of the four highest consecutive 15-second averages served as the value of $\dot{V}O_{2MAX}$, and was expressed per kg body mass. Heart rate and blood oxygen saturation (SpO_2) were recorded at each workload change.

Exercise Intervention Protocol

The training protocol design combined elements of previous exercise interventions in older women and men (Bingham et al., 1989; Pratley et al., 1994; Taaffe et al., 1995; Morio et al., 1998; Dionne et al., 2004; but especially Ryan et al., 1995; Hunter et al., 2000) and included both endurance and resistance components. During the 16-week intervention, Training group subjects attended the La Jolla YMCA on three non-consecutive days per week, for an approximately 1.5 hour session each

day. Sessions were segmented into warm-up, weight training, and cool-down periods. The warm-up began with a short (~5 min) stretching session, followed by 15 min aerobic exercise on an elliptical machine. Weight training consisted of 3 sets of 10-12 repetitions for each of ten exercises, performed on machines: abdominal crunch, arm curl, arm extension, chest press, lat pull-down, leg curl, leg extension, leg press, seated row, and trunk extension. The weight lifting exercises targeted major muscle groups with the overall goal of increasing muscle mass (e.g. Teixera et al., 2003), since skeletal muscle mass is thought to be a major factor underlying elevated REE (Zurlo et al., 1990; Bosy-Westphal et al., 2003; Krems et al., 2005). The cool-down consisted of 10 min exercise on the elliptical machine and a short stretching session.

Subjects scheduled seven one-on-one appointments with YMCA personal trainers, the first two occurring on the first two days of the intervention, followed by one appointment during each of the next two weeks, and then one every other week though week 11. At the first appointment subjects completed a submaximal strength test for each weight lifting exercise, which predicted one rep maximum (1RM). Depending on subject tolerance of discomfort, individual training programs were set up to begin at either 65% or 75% of 1RM. If subjects reported values ≥15 (hard) on the Borg Scale Rating of Perceived Exertion (RPE), initial workloads were set to 65% of 1RM; otherwise, workloads began at 75% of 1RM. During the second appointment trainers taught subjects the entire protocol, guiding subjects through proper stretching and lifting techniques to minimize risk of injury, and instructing them to work to failure to maximize strength benefits. Subsequent meetings focused on gauging subject progress and compliance, answering questions, and increasing weight lifting workloads if subjects had begun to reach maximum reps (12) without muscular failure.

Trainers were also available outside of these individual sessions to answer questions and help subjects if needed.

In addition to the weekly or bi-weekly “check-ins” with the trainers, subject compliance was monitored using an electronic key system with the elliptical and weight lifting machines (Wellness System Key, TechnoGym USA, Seattle, WA). Subjects inserted the key (which contained individual identification information) whenever they began work on a particular machine, recording date, time, duration and average resistance of elliptical exercise, and number of reps and amount lifted for each weight lifting set. Due to malfunctions and user error, however, sufficient data to assess rate of compliance exists for only 13 of 18 Training subjects. The 13 subjects with sufficient data exhibited 93% adherence to the protocol.

Statistical Analysis

Data were analyzed with SPSS version 16.0 for Windows. Variables included age (years), REE (kcal/d), physical activity level (times REE: xREE), $\dot{V}O_{2MAX}$ (ml O_2/kg/min), height (cm), weight (kg), waist and hip circumferences (cm), and body composition variables: body fat percentage, fat mass (kg) and fat-free mass (kg). Each variable at baseline was tested for normal distribution (Shapiro-Wilk test) and for outliers. These analyses were performed for both the pooled sample and within each of the Active and Training longitudinal study groups. Subsequent tests were run with and without outliers included to determine their effect on the outcomes. Where no differences in outcome occurred, the results are reported (below) with outliers included; where differences did occur, the reported results reflect the data as analyzed without the outliers. Missing values were not an issue for this study: only

0.4% of all data were missing. The longitudinal analysis used mixed-effects models (Diggle, 1989; Ridout, 1991) that can be fit with partially missing data (e.g. subjects with a few records missing), and that are valid under the missing at random assumption.

Cross-sectional analysis: Bivariate and partial correlation techniques were used to evaluate relationships between the study variables at baseline. These correlations were further investigated with multiple linear least squares regression analysis, including stepwise and hierarchical methods. Longitudinal analysis: Correlations within each group at baseline were examined in the same manner as in the cross-sectional analysis. Group means at baseline were compared by independent samples t-tests. Longitudinal data were analyzed using a linear repeated measures design (mixed effects model: Diggle et al., 1996) for the main effects of group, time, and the group x time interaction. Confounders as determined by the correlation and regression results were also controlled for in testing for group differences and for change in REE over time.

Power calculations for the longitudinal analysis were conducted pre-study using parameter estimates compiled from previous work (Pratley et al., 1994; Van Pelt et al., 1997, 2001; Adriaens et al., 2003; Gibbons et al., 2004). With 20 subjects per group, this study would have the statistical power (β=0.10, α=0.05) to detect a mean difference of ~125 kcal/d within the Training group over time, and a ~135 kcal/d difference between Active and Training groups at any one measurement time. Our actual recruitment almost reached the goal of 20 subjects per group: as noted above, the Active group N=19, and the Training group N=18.

Pilot Study of Postmenopausal Hadza Women's Physical Activity Level

Physical activity level was estimated for three older Hadza women, aged 51, 63 and 68, all of whom had ceased reproducing and nursing, and were thus thought to be postmenopausal (Alyssa Crittenden, personal communication). Foraging activity was recorded (by Alyssa N. Crittenden, Frank W. Marlowe, and colleagues) using focal-person follows for a total of 16 days between the three women (6 days each for the 51 and 68 year old women, 4 days for the 63 year old woman). Each focal follow began in the morning at camp and continued throughout the day until the individual being followed returned to camp. The researcher recorded the individual subject's activity at 5-minute intervals during the entire period of the follow. These 5-minute records were used to generate daily activity budgets for the three women, where each record was treated as representing 5 minutes of the recorded behavior.

The same methods for calculating physical activity level in the exercise study's subjects, outlined above, were used for the Hadza women. Time spent in individual categories of activity was summed for each day. Activities among the Hadza were assigned MET intensity values matched as closely as possible to activities listed in the compendium of Ainsworth et al. (2000): the common Hadza practice of digging for underground tubers, for example, was represented as "digging, spading, filling garden, composting…" (code 08050: Ainsworth et al., 2000), with a corresponding MET value of 5.0. The matches were, of course, somewhat imprecise, and so care was taken to use conservative estimates of energy expenditure, erring on the side of underestimation. Walking speeds were derived from GPS data in order to assign appropriate MET values for transport.

CHAPTER 5: RESULTS

Sample Characteristics

Baseline data for the pooled sample, as well as the Active and Training sub-samples, are displayed as box plots in Figure 5.1 (also see the Appendix, Table A.2). The sample exhibited considerable variation in exercise habits, as evidenced by the distribution of PAL values in the pooled sample and within the Active and Training groups. At baseline, the Active group had significantly higher $\dot{V}O_{2MAX}$ ($p<0.01$) and physical activity level ($p<0.01$), and lower body fat percentage as measured by dual-energy x-ray absorptiometry ($p=0.03$) than did the Training group (independent samples t-tests). The Active group also had ~7% higher REE (1278 kcal/d) at baseline than the Training group (1191 kcal/d), but this difference did not reach statistical significance ($p=0.09$).

Cross-Sectional Analysis of Baseline Data: Pooled Sample

The major associations of interest were all of the possible relationships between REE, age, body composition, and physical activity, as well as the relationship between REE and physical activity level after controlling for age and body composition. To minimize the number of variables in the cross-sectional correlation and regression analyses, fat-free mass, fat mass and body fat percentage were limited to only the measurements obtained using dual-energy x-ray absorptiometry. In the pooled sample, all body size/composition variables, aside from body fat percentage, were significantly and positively correlated with each other and with REE (see Table A.3 for all correlation coefficients and *p*-values). To reduce the number of inter-correlated body composition variables included in the models, stepwise

regression analysis was used to determine which factor(s) best explained variation in REE: fat-free mass was the best predictor of REE (r^2=0.540; p<0.01) and no other variables had significant effects on REE in the presence of fat-free mass. Moving forward in regression analysis of the pooled sample fat-free mass was the sole representative body composition variable used.

The following correlation results reflect Pearson's correlation (r) where both variables were normally distributed, or Spearman's correlation (r_s) where at least one variable was distributed non-normally. Age was significantly, negatively correlated with REE (r=-0.427; p<0.01), but not with fat-free mass (r=-0.264; p=0.10). Neither exercise variable, $\dot{V}O_{2MAX}$ and physical activity level, was significantly correlated with REE (respectively: r_s=0.076, p=0.67; r_s=0.240, p=0.15), age (r_s=0.003, p=0.99; r_s=0.251, p=0.12), or fat-free mass (r_s=0.073, p=0.67; r_s=0.144, p=0.38), but both were significantly, negatively correlated with fat mass (r_s=-0.567, p<0.01; r_s=-0.359, p<0.05) and body fat percentage (r_s=-0.774, p<0.01; r_s =-0.546, p<0.01). $\dot{V}O_{2MAX}$ and PAL were significantly, positively correlated with each other (r_s =0.636; p<0.01).

Multiple least squares linear regression analysis found that both fat-free mass and age significantly predicted REE (respectively: r^2=0.540, p<0.01; r^2=0.182, p<0.01; see Figures 5.2 and 5.3). Together, fat-free mass and age accounted for roughly 60% of the variation in REE (r^2=0.598, p<0.01). Hierarchical regression analysis was used to determine if exercise had a significant effect on REE after controlling for fat-free mass and age (Step 1), adding either $\dot{V}O_{2MAX}$ (Step 2a) or physical activity level (Step 2b) and testing for significant increases in the overall r^2 value (see Figure 5.4). Neither exercise variable significantly changed the regression coefficient, though the effect of physical activity level approached significance (p=0.07).

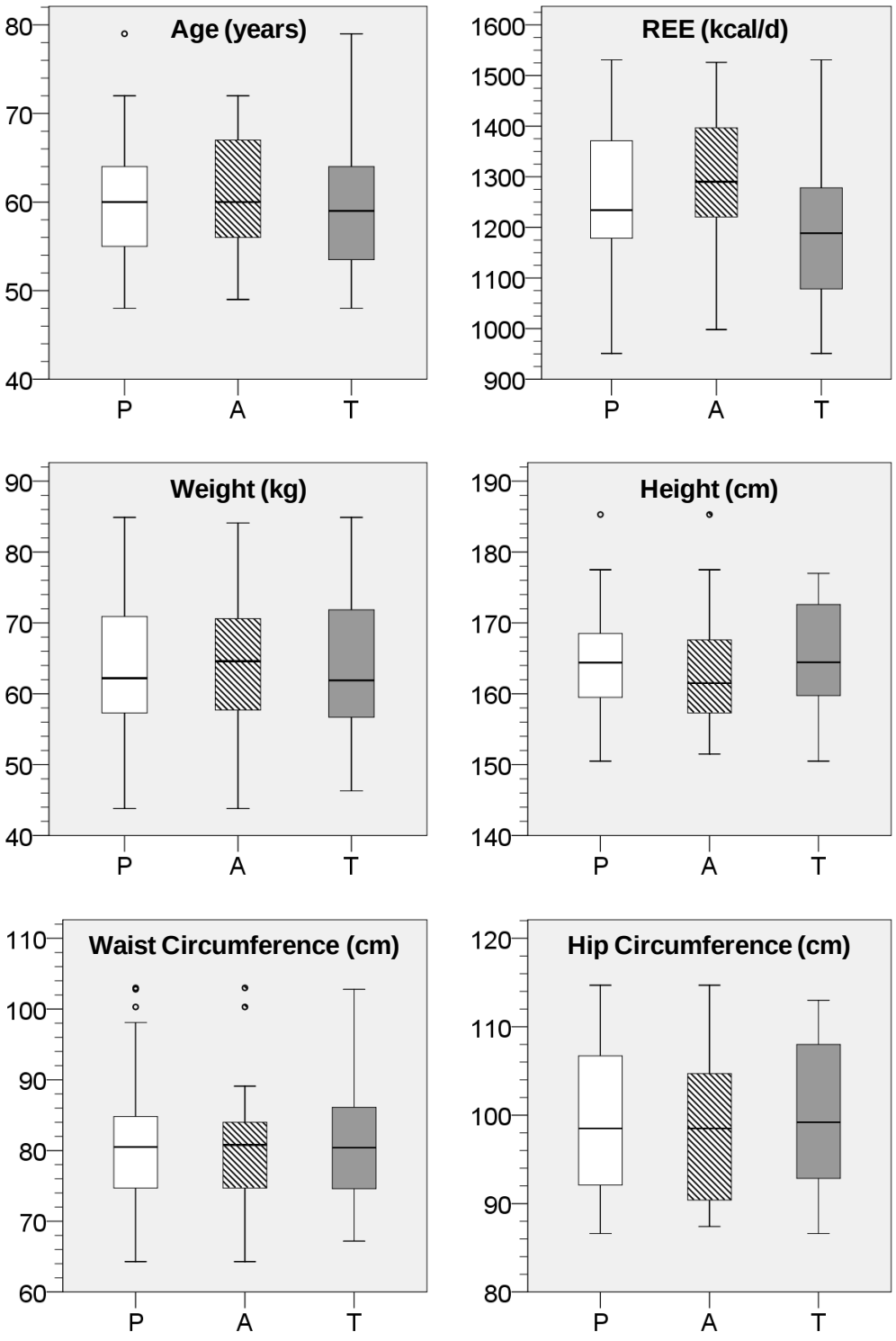

Figure 5.1: Baseline Pooled (P), Active (A) and Training (T) data

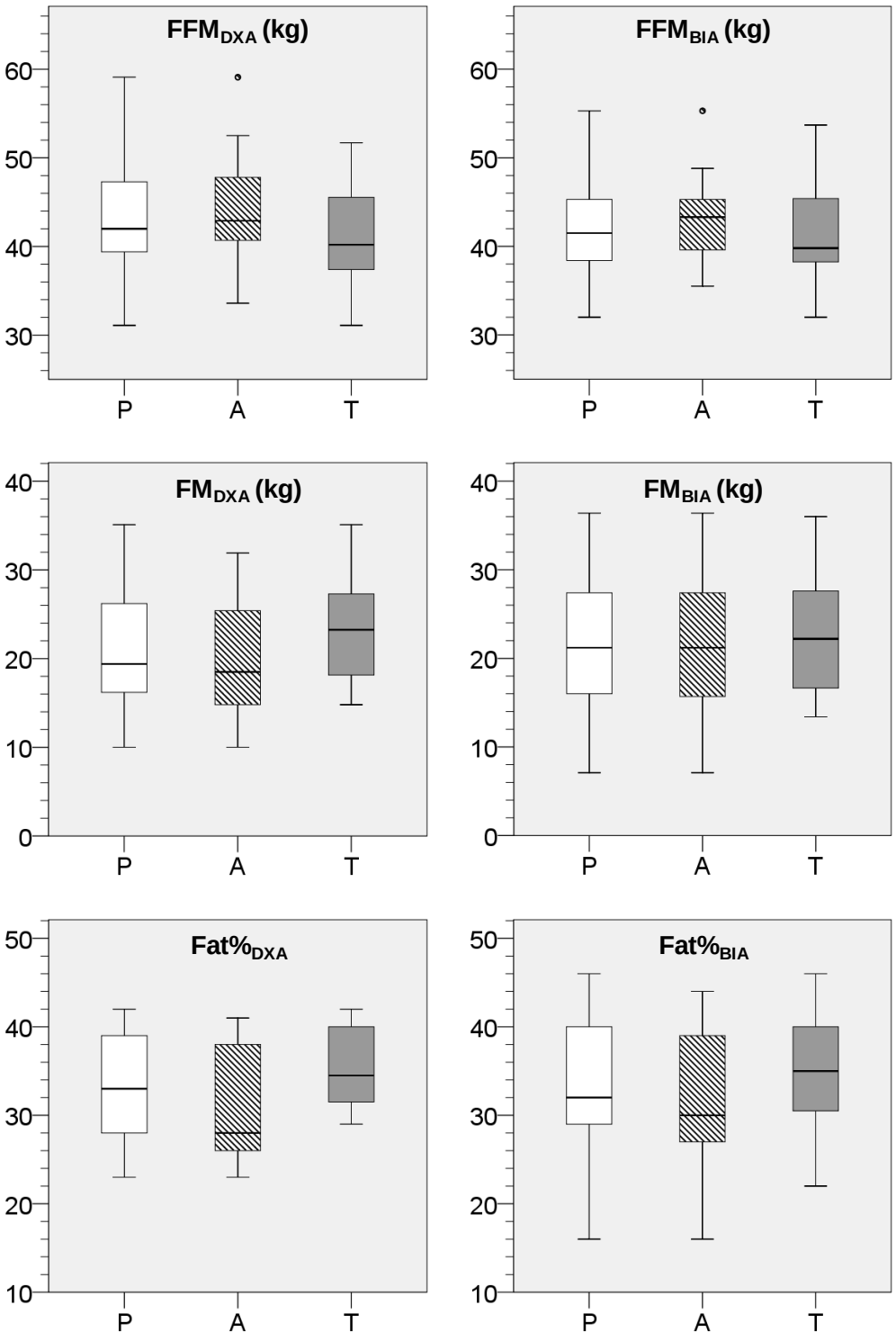

Figure 5.1 (continued): Baseline Pooled (P), Active (A) and Training (T) data

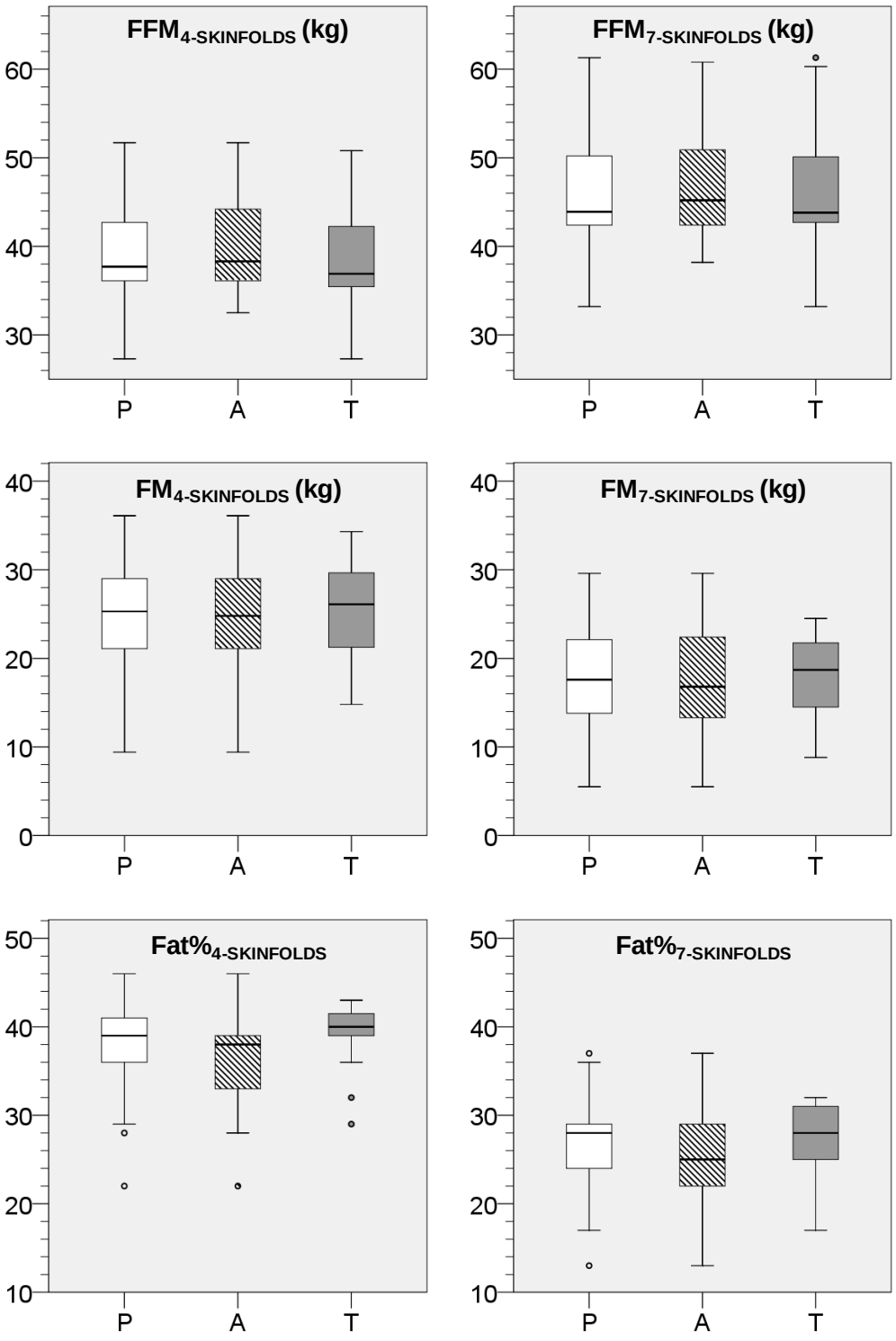

Figure 5.1 (continued): Baseline Pooled (P), Active (A) and Training (T) data

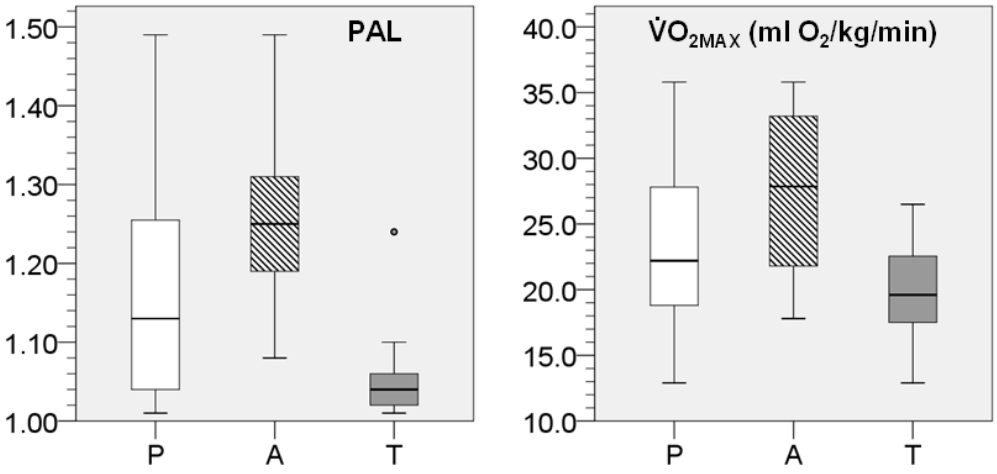

Figure 5.1 (continued): Baseline Pooled (P), Active (A) and Training (T) data

Notes: Box plots display median (dark bar within box), inter-quartile range (box), maximum and minimum non-outlier values (whisker ends) and outliers (circles, defined as those individuals falling further than 1.5 times the inter-quartile range from the 1st or 3rd quartile). Abbreviations are as follows: BIA=bioelectrical impedance analysis; DXA=dual-energy x-ray absorptiometry; Fat%=body fat percentage; FFM=fat-free mass; FM=fat mass; PAL=physical activity level; REE=resting energy expenditure; $\dot{V}O_{2MAX}$=maximal aerobic capacity.

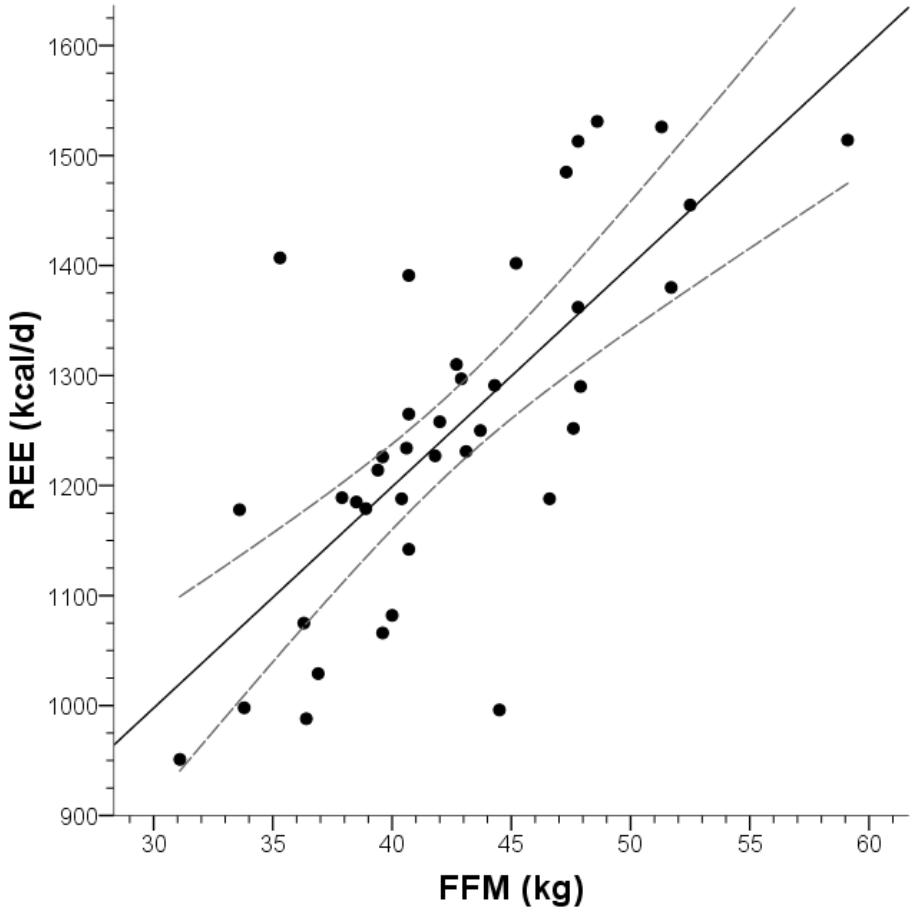

Figure 5.2: REE vs. FFM in the Pooled sample at baseline

Notes: Least squares linear regression (solid line; r^2=0.540; p<0.01) and 95% confidence interval of the regression (dashed lines). FFM=fat-free mass; REE=resting energy expenditure.

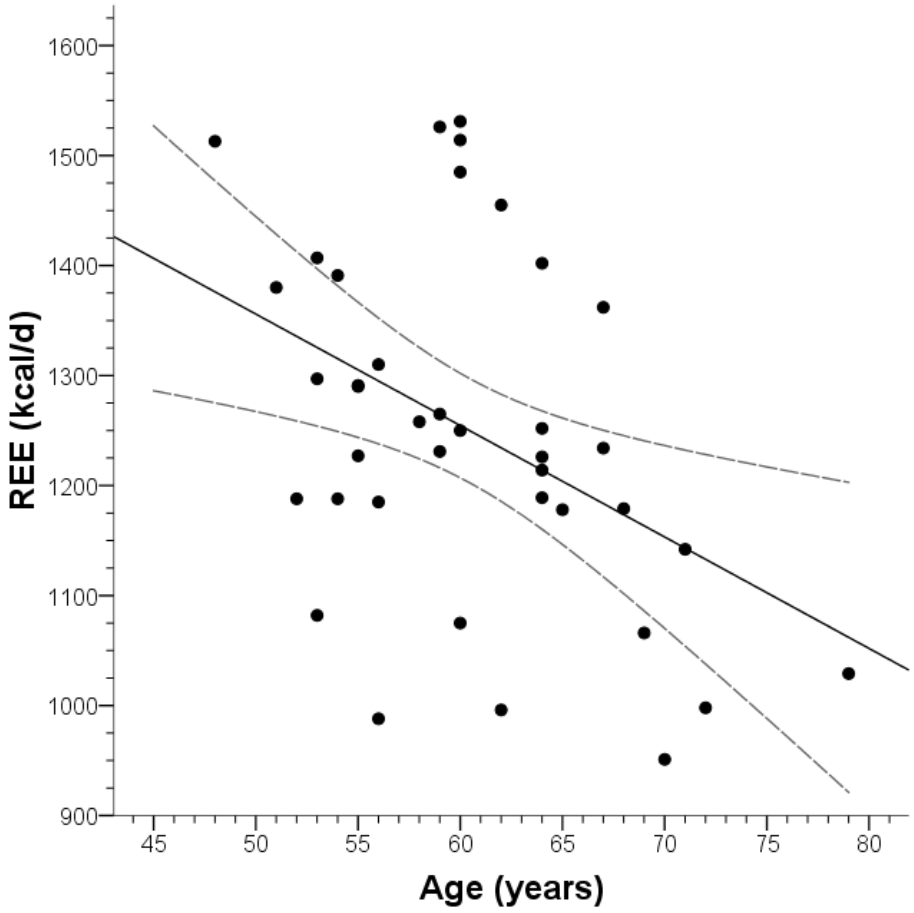

Figure 5.3: REE vs. age in the Pooled sample at baseline

Notes: Least squares linear regression (solid line; r^2=0.182; p<0.01) and 95% confidence interval of the regression (dashed lines). REE=resting energy expenditure.

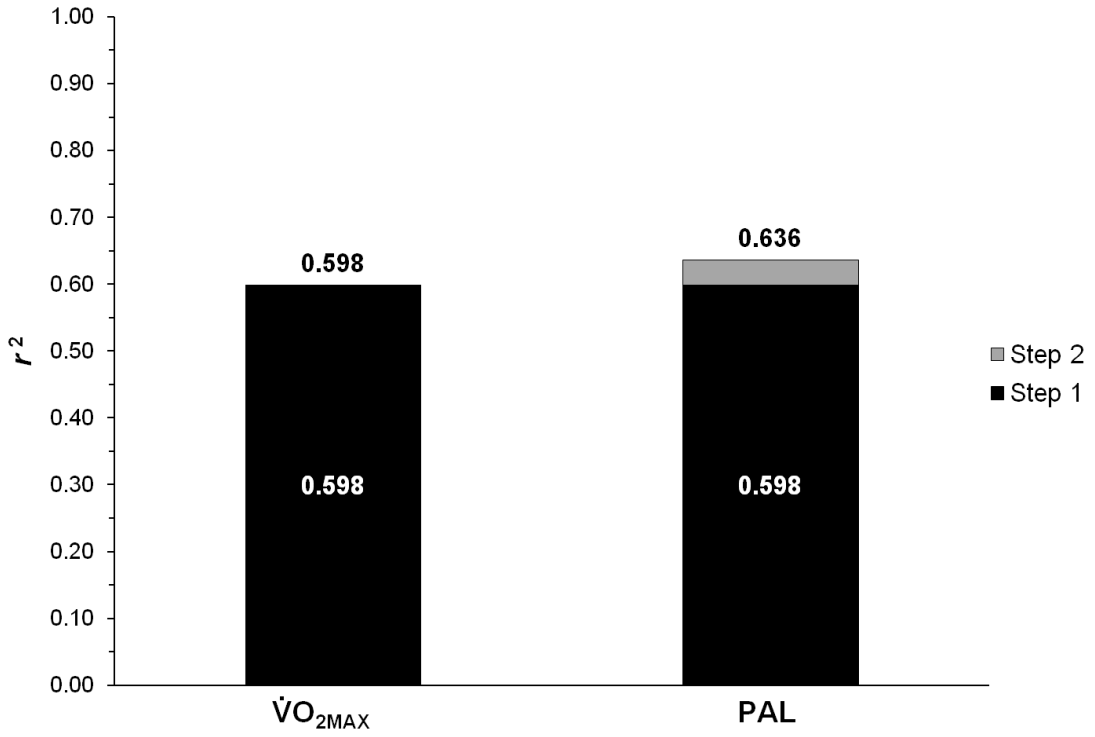

Figure 5.4: Hierarchical regression results in the Pooled sample at baseline

Notes: Step 1 independent variables were fat-free mass and age (r^2=0.598; p<0.01). Step 2 added either $\dot{V}O_{2MAX}$ (maximal aerobic capacity) or PAL (physical activity level) and tested for significant change to the F-statistic and r^2 values. Neither Step 2 addition significantly increased the r^2 value ($\dot{V}O_{2MAX}$ p=0.83; PAL p=0.07).

Longitudinal Analysis of Training Intervention: Active and Training Samples

Within the Active and Training groups, body size/composition variables were significantly and positively correlated with each other, as well as with REE (see Appendix, Tables A.4 and A.5), in a manner largely similar to the Pooled sample above. Analysis of covariance (ANCOVA) found no significant differences between the Active and Training groups for any of the baseline correlations between variables. The only variables for which the groups differed at baseline (Table A.2) were physical activity level (p<0.01), $\dot{V}O_{2MAX}$ (p<0.01), and body fat percentage (p<0.05) from dual-energy x-ray absorptiometry. The REE difference approached significance (p=0.09).

The repeated measures linear mixed models analysis found no significant effects of group membership, test time, or the group x time interaction on weight, height, hip circumference, fat-free mass (all four measures: dual-energy x-ray absorptiometry, bioelectrical impedance, four skinfolds, and seven skinfolds), or fat mass and body fat percentage derived from bioelectrical impedance (see the Appendix, Table A.6 for Active and Training group data at each test and statistical results). The same was true of REE, although in this case the group effect approached significance (p=0.07). In both groups, waist circumference and fat mass (from dual-energy x-ray absorptiometry) were significantly lower at 16 weeks than at baseline (p<0.05 for both); the groups did not differ significantly from one another for these variables, or for the manner in which they changed over time.

Fat mass from four and seven skinfolds and body fat percentage from seven skinfolds all changed significantly over time (time effect: for all $p \leq 0.01$). There was no group effect for these variables, but there were group x time effects (p<0.01 for both fat mass; p=0.02 for body fat percentage): the Active group had lower fat after 16 weeks, while the Training group changed very little. Body fat percentage from four skinfolds was lower in the Active group (p=0.04) and decreased over time in the Active group but not in the Training group (time effect: p=0.05; group x time interaction: p=0.01). Body fat percentage from dual-energy x-ray absorptiometry was also lower in the Active group (p=<0.05) but did not change over time (though the time effect approached significance: p=0.08). Finally, $\dot{V}O_{2MAX}$ differed between the two groups (p<0.01) and was slightly higher in both groups at 16 weeks compared to baseline (p=0.02). See Figures 5.5 through 5.8 for plots of group-specific means of selected variables over time (others are in the Appendix).

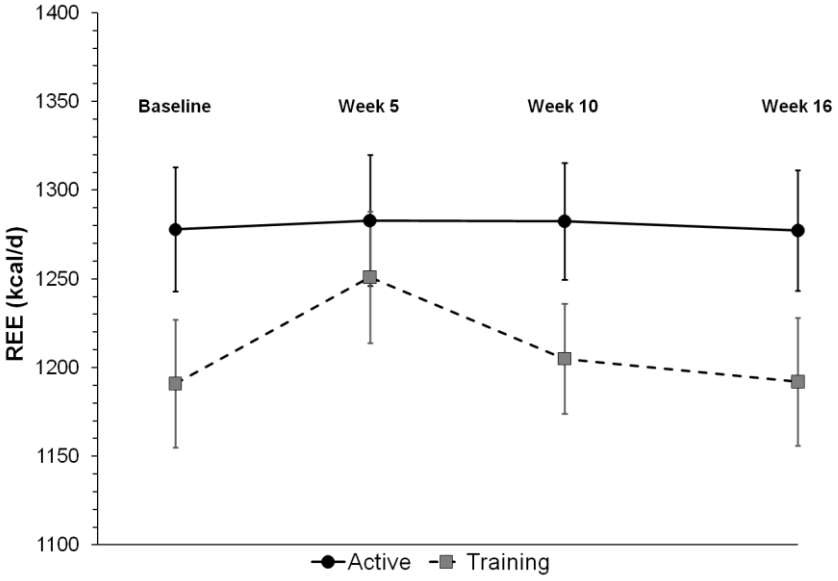

Figure 5.5: REE within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.07; time p=0.27; group x time p=0.40. REE=resting energy expenditure.

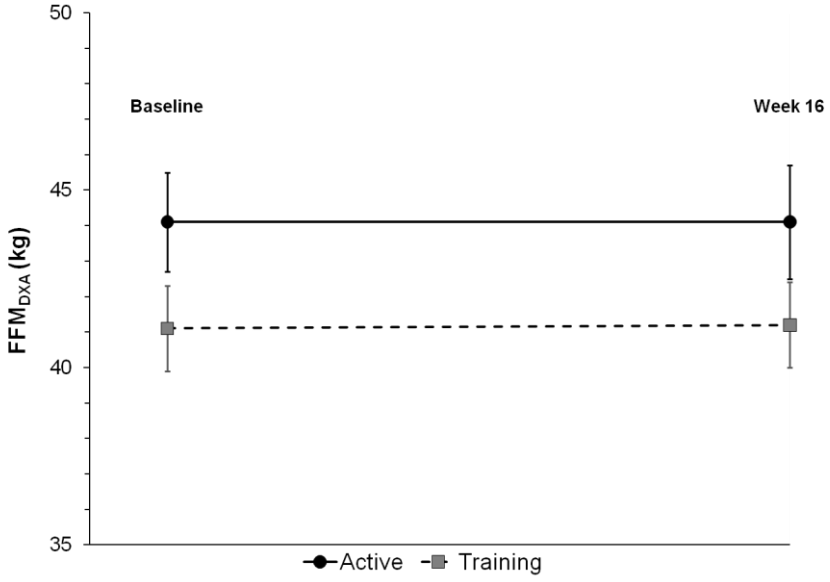

Figure 5.6: FFM_{DXA} within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.13; time p=0.71; group x time p=0.63. FFM_{DXA}=fat-free mass as measured by dual-energy x-ray absorptiometry.

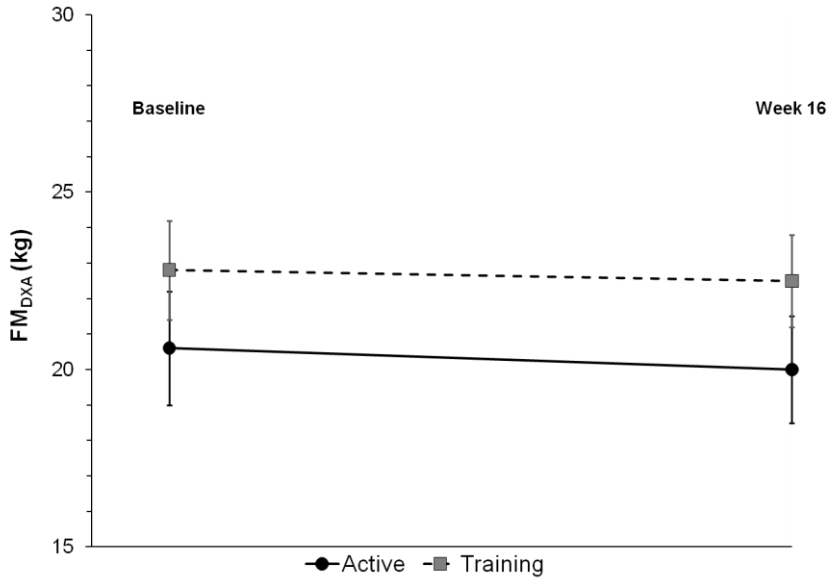

Figure 5.7: FM_{DXA} within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.25; time p=0.02; group x time p=0.40. FM_{DXA}=fat mass as measured by dual-energy x-ray absorptiometry.

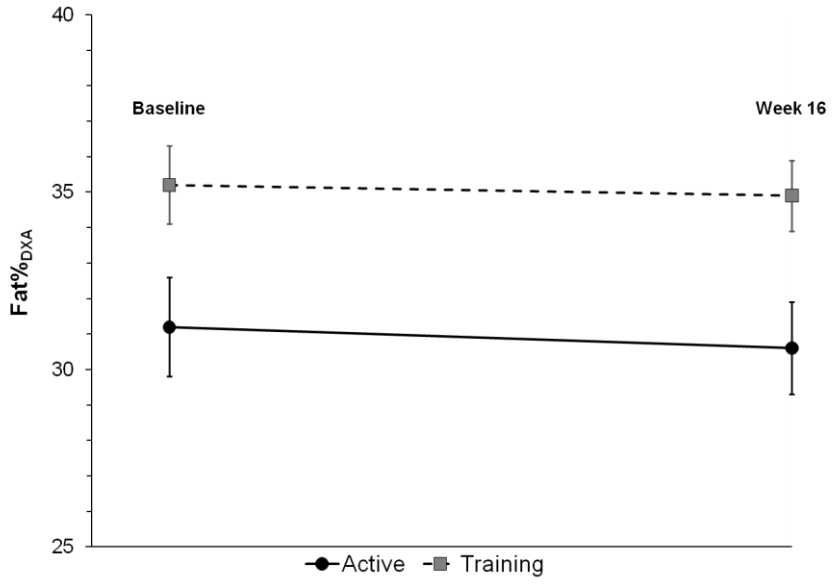

Figure 5.8: $Fat\%_{DXA}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.02; time p=0.08; group x time p=0.42. $Fat\%_{DXA}$=percent body fat as measured by dual-energy x-ray absorptiometry.

Follow-up Analysis: Trends in REE with age, fat-free mass and exercise

Overall, the results of both the cross-sectional and longitudinal studies showed no significant effect of either long-term or short-term physical activity on REE. The analyses did, however, produce very suggestive *p*-values for the relationship between exercise and REE, in particular for the r^2 change with the addition of physical activity level in the hierarchical regression analysis (p=0.07), the baseline comparison of mean REE between the Active and Training groups (p=0.09), and the group effect in the mixed models analysis (p=0.07). These values all approach significance, indicating the possibility that the sample sizes were too small and that the study was therefore underpowered and prone to type II error (i.e. the failure to reject a null hypothesis—here that exercise has no effect on REE—when that hypothesis is in fact not true). While the sample size is likely an issue, an alternative (though not mutually exclusive) possibility is that there is a "threshold effect" of exercise, where activity only above a certain level exerts any influence on REE. It is quite possible that the exercise habits of many subjects would fall below such a threshold, should it exist, and so this warranted further investigation.

Figure 5.9 is a plot of REE vs. age for the Active and Training groups: because there was no change over time, the REE values used in the following discussion and figures are individual averages of all four measurements. The negative relationship between REE and age was significant in the Training group (r^2=0.435; p<0.01) but not within the Active group (r^2=0.124; p=0.14), though analysis of covariance found no significant difference between the groups for the REE/age relationship (group x age interaction: p=0.51). What is particularly interesting about this plot, however, is the group of five Active women (circled) whose REE values fall

well above the rest of the subjects within their age range. Not only do they appear to exert a strong effect on the REE/age relationship in the Active sample, they may also provide evidence for an intensity threshold for the effects of exercise on metabolic physiology. Given that the Active sample was quite variable for physical activity level, if these five women happen to be on the *most* active end of that distribution, it may say something about the prospects of finding an exercise effect on REE in future studies of larger samples.

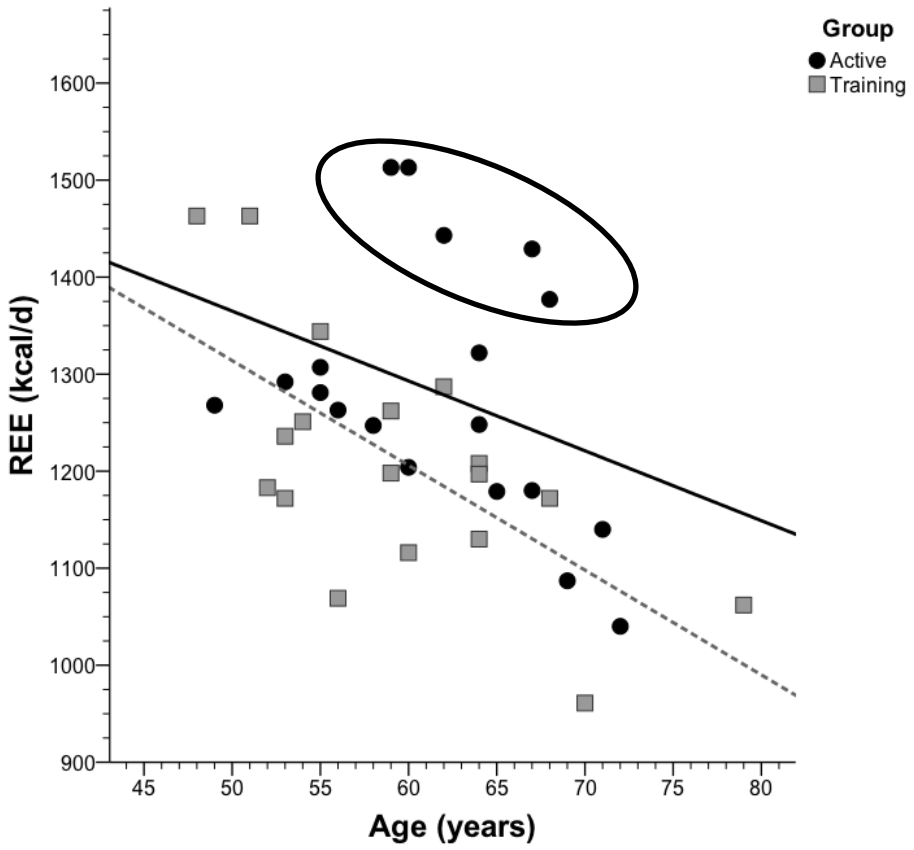

Figure 5.9: Individual average REE vs. age in the Active and Training groups I

Notes: REE (resting energy expenditure; average of four measurements) vs. age in the Active and Training groups. Regression lines: Active (solid line: r^2=0.124; p=0.14); Training (dashed line: r^2=0.435; p<0.01). Circled subjects have high REE for age, and are all members of the Active group.

To test whether these subjects' high REE values related to exercise, a regression equation predicting REE from age (r^2=0.195; p<0.01) was derived from all subjects. The Active subjects' REE-for-age residuals were then plotted against fat-free mass and physical activity level to assess body size and exercise effects. The REE residuals were significantly and positively related to fat-free mass (r^2=0.742; p<0.01; see Figure 5.10), but not to physical activity level (r^2=0.096; p=0.19; Figure 5.11). Physical activity level was not significantly correlated with fat-free mass (r^2=0.095; p=0.20; Figure 5.12). Even controlling for fat-free mass, physical activity and residual REE were not significantly correlated (r=0.092; p=0.72).

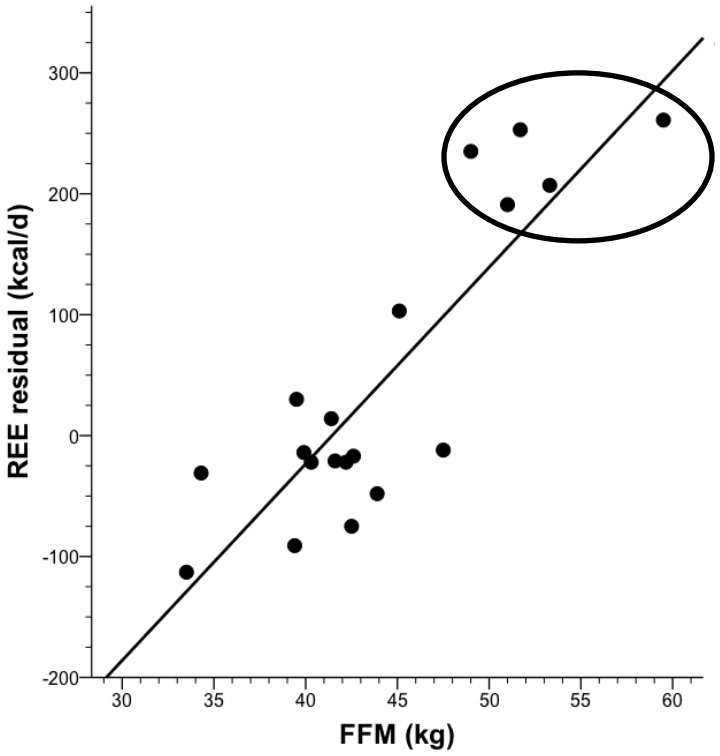

Figure 5.10: REE-for-age residuals vs. FFM in Active subjects

Notes: REE (resting energy expenditure)-for-age residuals vs. FFM (fat-free mass) in the Active group: r^2=0.742; p<0.01. Circled subjects: see Figure 5.9 notes.

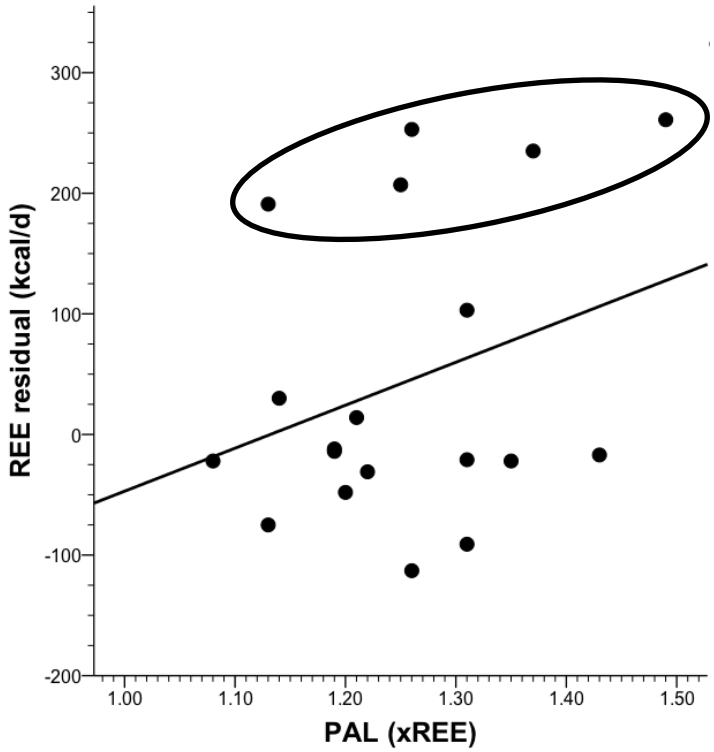

Figure 5.11: REE-for-age residuals vs. physical activity level in Active subjects
Notes: REE (resting energy expenditure)-for-age residuals vs. PAL (physical activity level) in the Active group: r^2=0.096; p=0.19. Circled subjects: see Figure 5.9 notes.

Taken together, these findings show that body size, as represented by fat-free mass, explains the five Active subjects' high REE-for-age residuals. There is no corresponding effect of physical activity on REE, even indirectly via a relationship with fat-free mass. Thus, these five women exhibit high REE simply because they also happen to be large people: they have the five highest fat-free mass values in the entire pooled dataset, and three of them were the three tallest women in the study. When the data are plotted again with these five subjects removed, the REE vs. age regression relationship within the Active group reaches significance (Figure 5.13), and again, the two groups do not differ for the REE-age relationship (p=0.70).

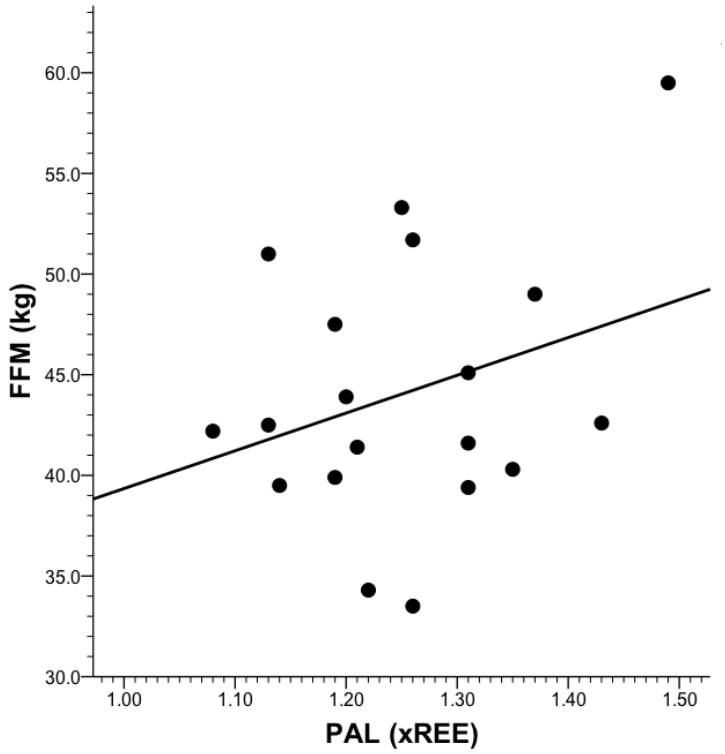

Figure 5.12: FFM vs. physical activity level in Active subjects

Notes: FFM (fat-free mass) vs. PAL (physical activity level) in the Active group: r^2=0.095; p=0.20.

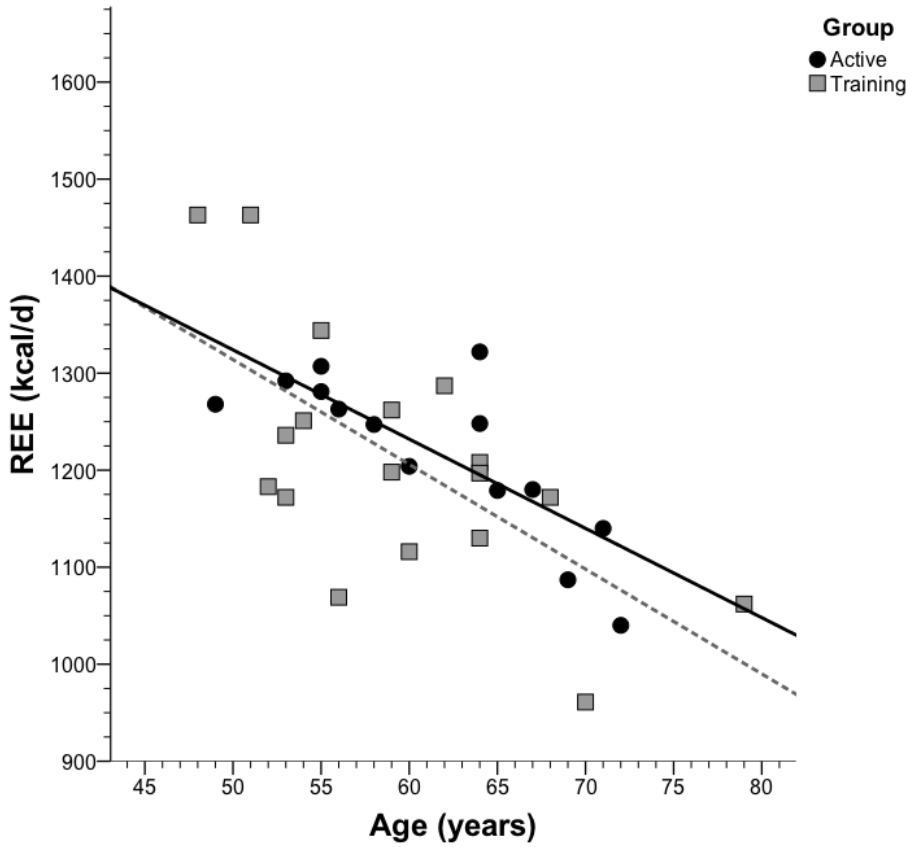

Figure 5.13: Individual average REE vs. age in the Active and Training groups II
Notes: REE (resting energy expenditure; average of four measurements) vs. age in the Active and Training groups, with the five heaviest Active subjects removed (circled in Figure 5.9). Regression lines: Active (solid: r^2=0.615; p<0.01); Training (dashed: r^2=0.435; p<0.01).

Physical Activity Level in Postmenopausal Hadza Women

The pilot study found the three postmenopausal Hadza women to be quite active, with physical activity values for foraging days ranging from 1.22 to 2.16 xREE, and clustering largely between 1.5-1.8 xREE around a mean of 1.65 (see Figure 5.14). Individual mean values were 1.68, 1.62 and 1.64 xREE for the women aged 51, 63 and 68 years, respectively. These physical activity values are quite similar to estimates for adult women of all ages in the Ache and !Kung hunter-gatherer groups

(from Leonard and Robertson, 1992), but are considerably higher than estimates for the Training and even the Active subjects (see Figure 5.15). Although the physical activity level values for the exercise study's subjects are likely slight underestimates, the values for the Hadza women may also be low since the factorial method used here tends to underestimate daily energy expenditure, especially in highly active individuals (Leonard et al., 1997). Thus, the gap between women in hunter-gather and industrialized societies may be slightly greater even than shown here.

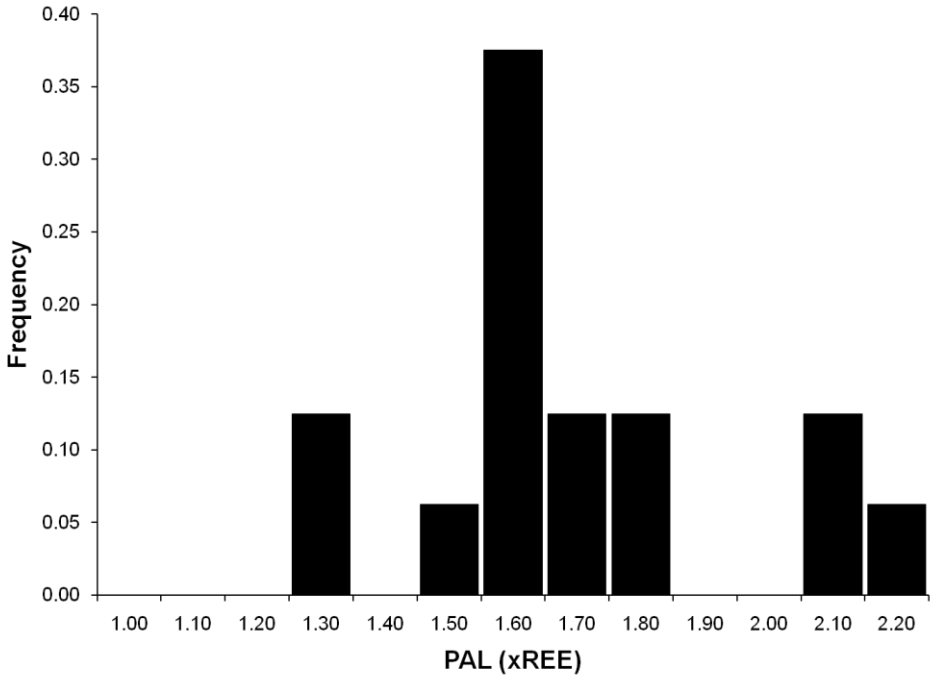

Figure 5.14: Distribution of daily physical activity level in three postmenopausal Hadza women

Notes: Physical activity level (PAL) as a multiple of resting energy expenditure (xREE) estimated for three postmenopausal Hadza women, representing 16 total days of foraging. PAL was estimated using activity budgets derived from unpublished focal-person follow data collected by Frank W. Marlowe, Alyssa N. Crittenden and colleagues.

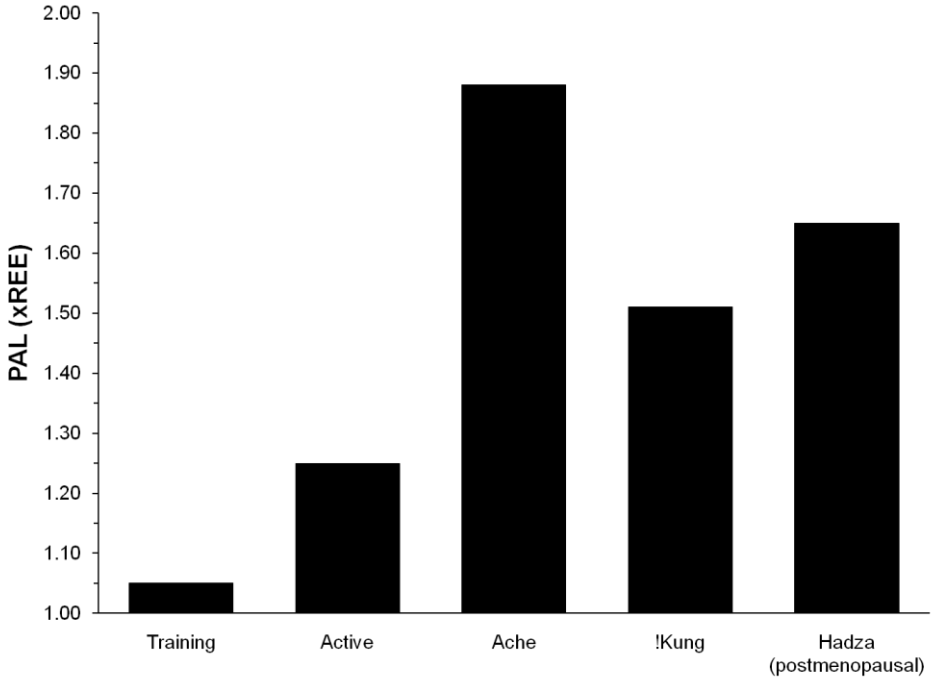

Figure 5.15: Physical activity in Training, Active and hunter-gatherer women

Average physical activity level (PAL) as a multiple of REE (xREE) in this study's Training and Active samples, compared to hunter-gatherer women. Hunter-gatherer data were derived from activity budgets. Ache and !Kung values are for adult women of all ages, from Leonard and Robertson (1992). Hadza PAL represents the mean of 16 foraging days among 3 postmenopausal women (ages 51, 63, and 68 years) from focal follow records of foraging activity (unpublished data: Frank W. Marlowe, Alyssa N. Crittenden and colleagues).

CHAPTER 6: DISCUSSION AND CONCLUSIONS

Contrary to expectations, there appears to have been no effect of the study's training regime on body composition or metabolic physiology in this sample. Moreover, despite an inverse correlation between exercise and body fat, physical activity seems to have had no effect on REE even in the Active sample. Returning to the study's stated hypotheses, the first predicted that exercise would ameliorate the age-related decline in REE: this is rejected. In our sample, REE was significantly, negatively correlated with age, even after controlling for body composition, and there was no significant effect of exercise on those relationships. The absence of an exercise effect renders the second hypothesis moot: although there are significant correlations between REE and all body composition variables, in particular fat-free mass, these do not bear any relationship to level of exercise as approximated by physical activity level and VO_{2MAX}. Finally, the results support the third hypothesis that age-specific REE would associate similarly with both short- and long-term exercise, but only in the sense that *neither* exercise regime affected REE.

It is interesting that no changes in body composition or REE occurred despite clear training effects. For example, in the 13 Training subjects with sufficient data, the average amount of weight lifted per exercise session (total of all repetitions for ten exercises) increased significantly from 10,784 kg during the first 5 weeks to 12,402 kg during weeks 5-10, and 13,382 during weeks 10-16 (see Figure 6.6; one-way repeated-measures ANOVA, overall $p<0.01$; Tukey HSD post hoc test: weeks 5-10 and 10-16 both greater than weeks 0-5, $p<0.05$ and $p<0.01$, respectively; weeks 5-10 and 10-16 not significantly different). In addition to this strength effect, subjects also had significantly increased aerobic fitness at 16 weeks vs. baseline (paired samples t-

tests), as evidenced by higher $\dot{V}O_{2MAX}$ (1.35 ± 0.07 l O_2/min vs. 1.27 ± 0.07 l O_2/min; p<0.01), and higher $\dot{V}O_2$ (1.22 ± 0.06 l O_2/min vs. 1.10 ± 0.06 l O_2/min; p<0.01) and workload (in watts: 101.6 ± 5.4 W vs. 82.2 ± 6.1 W; p<0.01) at the ventilatory threshold (which marks the workload at which an individual can maintain prolonged, aerobic endurance exercise: Wasserman et al., 2004). Ventilatory threshold $\dot{V}O_2$ as a percentage of $\dot{V}O_{2max}$ also increased (91 ± 0.09% vs. 87 ± 1.4%), but the change did not reach significance (p=0.07).

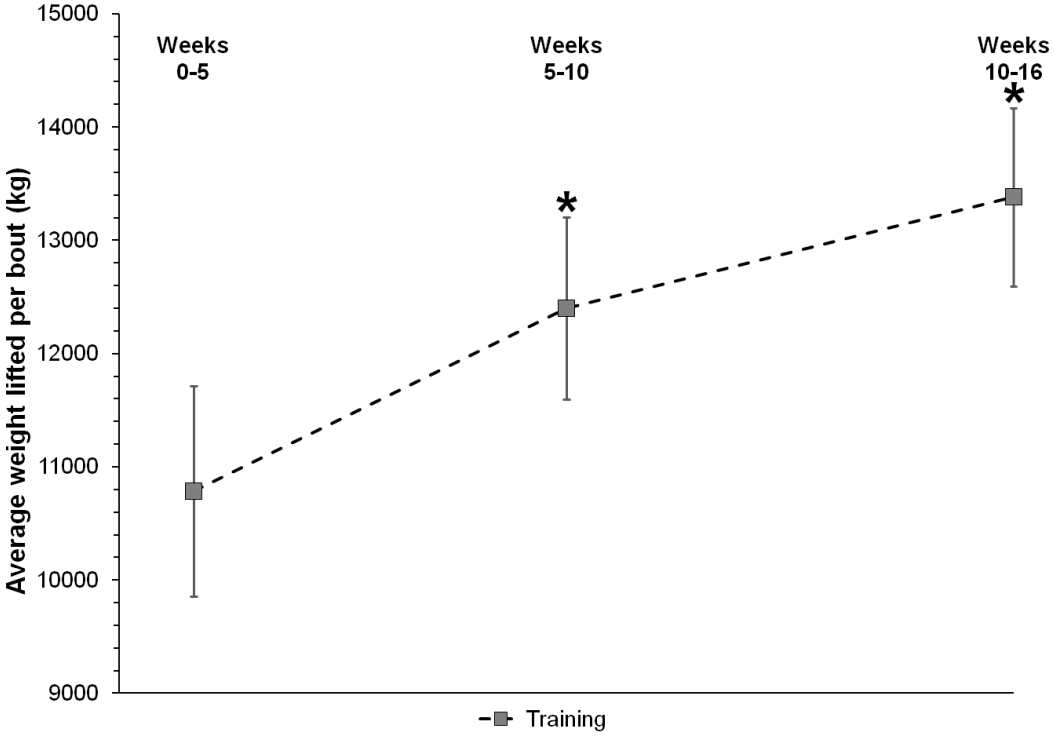

Figure 6.1: Average total weight lifted per bout in the Training group

Notes: Average total weight lifted per exercise bout (total for all repetitions of ten exercises) during weeks 0-5, weeks 5-10, and weeks 10-16. One-way repeated-measures ANOVA: p<0.01; post hoc Tukey HSD: weeks 5-10 significantly greater than weeks 0-5 (p<0.05); weeks 10-16 significantly greater than weeks 0-5 (p<0.01); weeks 5-10 and weeks 10-16 not significantly different.

The absence of an effect of exercise on REE in this study's sample, despite clear aerobic and muscular training effects, mirrors results of previous interventions that lasted 14-15 weeks (Taaffe et al., 1995; Morio et al., 1998), 6 months (Thompson et al., 1997; Dionne et al., 2004; Santa-Clara et al., 2006), or even a full year (Taaffe et al., 1995). It is unclear why the present study failed to reproduce the results of Ryan et al. (1995) and Hunter et al. (2000), where subjects significantly increased muscular strength, fat-free mass and REE with either 16 weeks or 6 months of resistance training, respectively. This is particularly odd given that the training intervention to a large extent followed their methods. There are limitations to the previous studies' treatment of their samples, however, that may undermine the generalizability of their results. Ryan et al. (1995) studied two small sub-groups of subjects that separately exhibited no significant change in REE, but when pooled together did—the fact that these groups completed different interventions raises questions about the validity of the pooled results. Additionally, the changes in fat-free mass and REE that Ryan et al. (1995) report are marginal, falling within one standard error of the mean for each variable. Hunter et al. (2000) examined a mixed-sex sample, and did not report separate data for the men and women in their study. Although they stated that the results did not differ between the sexes, they rightly noted that their samples (8 women, 7 men) were likely too small to detect sex differences anyway. It remains possible that if Hunter et al. (2000) had analyzed only the women in their sample, they would have found different results.

In comparison to previous intervention studies, neither the length of the present study's training program, nor its design appear to explain the absence of changes in fat-free mass or REE with increased exercise. Sample size for the

present study could be a problem, but the present sub-samples were larger than in any of these previous studies, for which within-groups samples ranged from N=7 to N=15. Thus, the present study was better-powered to detect differences than any of these previous interventions, and yet still found none. While this study's Training group N of 18 subjects is still a small sample, given that the magnitude of change in mean REE from baseline to 16 weeks was 1 kcal/d (1191 to 1192 kcal/d), it is quite reasonable to conclude that the intervention truly did not affect REE.

What is especially interesting is that the Active group did not differ from the Training group for REE, and that both groups fell on the low end of the range of fat-free-mass-specific REE values for sedentary subjects in previous intervention studies (this study, both groups: 29 kcal/kg/d; previous studies: 29-33 kcal/kg/d). When compared to the active women in the study of Van Pelt et al. (1997), this suggests that not only was the present study's exercise intervention insufficiently intense, but the definition of "active" as a criterion for inclusion in the Active group may have been too lax. Again, Van Pelt et al., (1997) included only highly trained, elite postmenopausal athletes in their sample, while in the present study, women who walked 5 hours per week and had been doing so for at least 10 years were defined as "active". For comparison, Figure 6.2 adds the physical activity level of athletes from Van Pelt et al. (1997; physical activity level was not measured, and so was estimated from $\dot{V}O_{2MAX}$ using the relationship in the present study's Active subjects) to the plot of the present study's subjects and hunter-gatherers. Clearly, the amount of exercise in which the highly trained athletes habitually engage is more in keeping with physical activity levels among hunter-gatherer women.

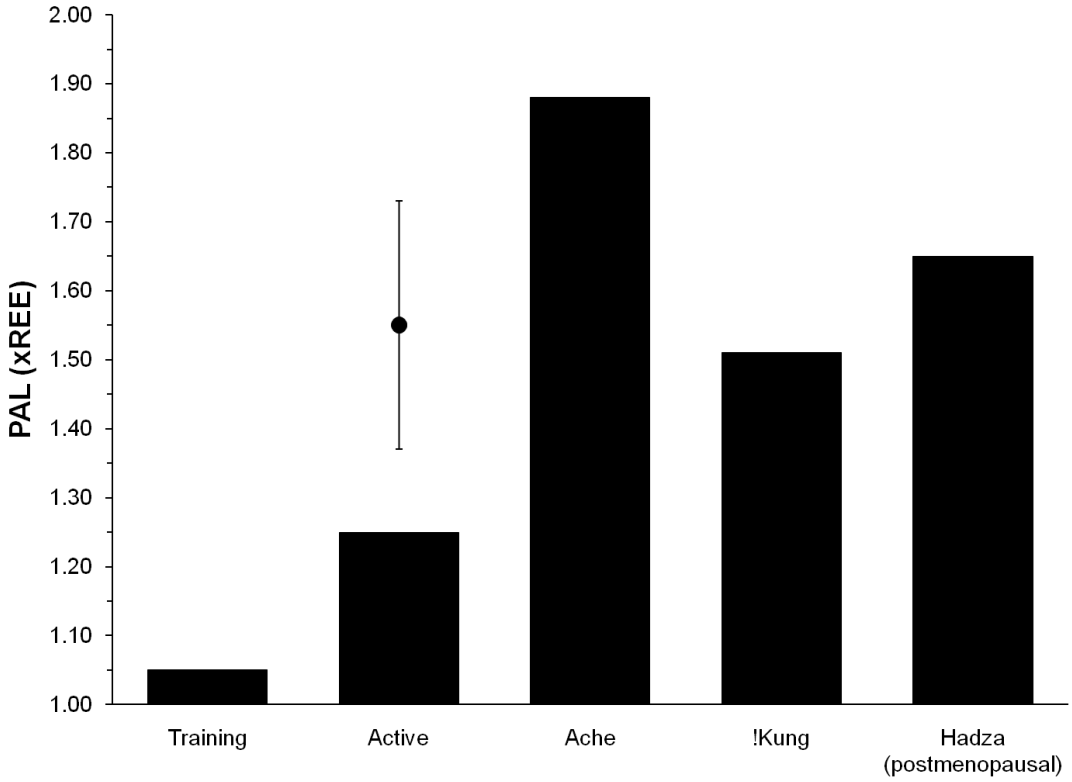

Figure 6.2: Postmenopausal athletes (Van Pelt et al., 1997) compared to this study's subjects and hunter-gatherer women

Average physical activity level (PAL) as a multiple of REE in this study's Training and Active samples, compared to postmenopausal athletes from Van Pelt et al. (1997; circle with error bars, as calculated from $\dot{V}O_{2MAX}$; circle is for the weighted mean of runners and swimmers, error bars represent means for runners on the upper end, and swimmers on the lower end) and to hunter-gatherer women. See Figure 5.15 notes for hunter-gatherer data sources.

As Van Pelt et al. (1997:3212) state, their "…results do not address the question of the minimum level of habitual exercise that is associated with a diminished age-related decline in [REE]." (Van Pelt et al., 1997:3212) Here, more moderate exercise has been shown to have no effect on REE, consistent with the idea that there may be some kind of threshold below which exercise does not provide benefits to postmenopausal women in terms of REE. The same threshold effect may

also relate to the ability to maintain body composition and metabolic health into older age. Runners from Van Pelt et al. (1997) had only slightly higher mean body fat percentage (23.3%, from hydrodensitometry) than the three postmenopausal Hadza women in the present study (19.6%, from bioelectrical impedance), or even compared to younger Hadza women who in general have a very low body fat percentage of ~19% which they maintain throughout adulthood, across the menopausal transition, and into the eighth decade of life (Sherry and Marlowe, 2007). Meanwhile, the present study's Active sample had mean body fat of 32.8 ± 1.8% (range of 20-43%; bioelectrical impedance). Although factors like diet may also be important, moderate exercise in the Active sample coincides with higher body fat and lower REE.

In addition to a threshold effect for intensity of exercise *after* menopause, there may be a similar, menopause-related time threshold after which the effects of exercise on metabolic health are diminished. Hunter-gatherers maintain high levels of activity across adult life and throughout the menopausal transition, and thus the continuing function of metabolic systems into the postmenopausal period may be primed to respond best to conditions of sustained physical exertion across the adult years. Instead, physical activity tends to decline with age in industrialized populations (Crespo et al., 1996), and this increasingly sedentary lifestyle with age may impair the musculoskeletal response to exercise and perhaps, by proxy, the metabolic effects of exercise. This is especially relevant to the Training subjects in the present study who transitioned into postmenopausal life in a very sedentary state, but may also apply to Active subjects on the lower end of their group-specific physical activity scale.

A growing body of evidence is beginning to make connections between the direct physiological effects of exercise on muscle and bone and broader systemic

changes in metabolic regulation and disease. The topic of age-related changes in these factors is a major focus of such work, and there is support for an age-related threshold beyond which the exercise response weakens. For example, the growth hormone/insulin-like growth factor-I (GH/IGF-I) axis forms part of a hormonal pathway that, among other functions, prevents muscular atrophy and promotes the muscular response to exercise (hypertrophy and angiogenesis), which may increase metabolic activity and oxygen consumption in muscle (Lynch et al., 2001; Rommel et al., 2001; Hunter et al., 2004; Moran et al., 2007). Low levels of serum IGF-I are also linked to risk for diseases such as ischemic stroke and heart disease, and to obesity, insulin resistance, and impaired glucose tolerance (Rasmussen et al., 1995; Juul et al., 2002; Sandhu et al., 2002; Johnsen et al., 2005). Results of various studies suggest that GH/IGF-I activation with resistance exercise differs between pre- and postmenopausal women, such that training significantly increases serum IGF-I concentrations in women aged 18-23 years (Koziris et al., 1999; Marx et al., 2001), but not in sedentary women aged 39-64 (Sillanpää et al., 2010).

This suggests that reduced GH/IGF-I muscle response may develop as early as the peri-menopausal period and the onset of changes in reproductive hormones. In postmenopausal women, although resistance exercise often increases muscle fiber size in sedentary postmenopausal women it is not necessarily accompanied by increased basal serum IGF-I (Häkkinen et al., 2001). A similar pattern of reduced exercise response with sedentary aging may exist for vascularization and angiogenesis in muscle, though current data are limited (Harris, 2005). If accurate, however, this suggests that in addition to impaired GH/IGH-I functionality, disuse of muscles with age might result in lost capacity for expanding capillary networks along

with muscle fiber growth, which may restrict oxygen delivery to muscle and thus affect muscle metabolic rates.

Finally, exercise and metabolic health also appear to be connected to telomere length, which, again, can be considered as a molecular "clock" of physiological aging (Demerath et al., 2004). Various studies have found links between leukocyte telomere length and risk factors for metabolic and cardiovascular disease, including a positive association between telomere length and blood IGF-I (Barbieri et al., 2009; Kaplan et al., 2009). Two studies point to the importance of physical activity and body composition on the relationship between aging and telomere length. Cherkas et al. (2008) showed that more active people tend to have longer telomeres after controlling for confounders including age; this study also included a comparison of twins with different activity habits, in which they found the more active twins to have significantly longer telomeres than their counterparts. Thus, exercise appears to associate with "younger" looking telomeres, which also correlate with better metabolic and cardiovascular health.

Gardner et al. (2005) conducted a longitudinal follow up study, studying the same individuals first in their late 20/early 30s, and then again in their late 30s/early 40s. The rate of telomere shortening was greater in subjects who also had higher body mass index (BMI) and greater evidence of impaired glucose regulation. Interestingly, three subjects actually had *longer* telomeres at the follow up test, and two of them also had lower BMI and reduced insulin resistance. While Gardner et al. (2005) do not report directly on exercise, the change in BMI in their subjects is suggestive: for the most part it points in the direction of reduced exercise, but in those

two cases possibly indicates an increase in exercise. Implicitly emphasizing the importance of exercise, they state:

> "It has been proposed that (excluding pregnancy), 'not gaining weight after early adulthood' may serve as an epidemiological paradigm of caloric restriction in humans [Lee et al., 2003]. Accordingly, gain in body mass (primarily due to adiposity) may hasten biological aging. *Because body fat reflects not only caloric consumption but also energy expenditure, the 'not-gaining-weight' model is not strictly caloric restriction*." (emphasis added)

In other words, exercise is important, and so may be its timing after early adulthood. In the aforementioned study of Dionne et al. (2004), premenopausal women not only increased fat-free mass and REE with exercise, but also improved glucose metabolism; the postmenopausal sample did not. Again, these findings are consistent with the idea that sedentary aging impairs the metabolic response to exercise. This is relevant to determining the utility of exercise interventions in sedentary postmenopausal women if they may have already passed a "use it or lose it" threshold, and thus may be less able to improve metabolic function through exercise. If real, such a threshold could explain this study's Training group's strength and aerobic adaptations to exercise without associated increases in muscle or REE.

Limitations

Before concluding, it is important to point out some limitations of the current study in its attempt to elucidate the relationship between exercise, metabolic physiology, aging, and the evolution of the human postmenopausal lifespan. For one, the cross-sectional nature of the study with regard to age limits its interpretability with

regard to any age-related declines. While the data do show that older women in the sample tended to also have lower REE, this does not mean that each individual woman had lower REE than they did at earlier ages and prior to menopause. It is entirely possible that the habitually active women in this sample have maintained REE at a level similar to their younger years, while the sedentary women of the Training sample could have had significantly higher REE when they were younger. It is impossible to evaluate that possibility in this sample, but should definitely be addressed in future longitudinal work.

A related limitation is the absence of a control group that remained sedentary throughout the 16-week study. The protocol originally called for the inclusion of such a group, but logistical considerations required that arm of the study to be dropped. The possibility remains that such a control group could have exhibited *decreased* REE over the course of the study, so that the lack of change in the Training group would instead have been characterized as an absence of decline. Given that the study lasted only 4 months, however, and that cross-sectional estimates of age-related decline in REE are generally on the order of ~2-5% per *decade*, the visibility of REE decline in a control group would have likely been quite minimal.

Also important is the fact that despite lower REE associating with increased age in this sample, and the absence of a metabolic response to exercise, these women were all healthy, non-obese, and free from metabolic and cardiovascular health problems. This detracts from the argument that exercise is necessary to maintaining normal metabolic and cardiovascular function in postmenopausal women. That is not to say, however, that none of these women is at risk for developing such problems in the future. As noted above, body fat percentage, which is a risk factor for

metabolic and cardiovascular disease, was quite high even in the Active group, meaning that many of these women may be at risk for developing the metabolic syndrome (Zhu et al., 2003). Still, in terms of disease risk and somatic maintenance, these women appear to be functioning quite well regardless of their exercise levels, which points to the possible influence of other, non-activity factors.

Those other possible factors, in particular demographic and lifestyle variables that differentiate industrialized populations from hunter-gatherer societies, also present limitations for the present study. Diet, for example, was not controlled, either in terms of dietary history or in terms of what subjects consumed during their participation in the study. Thus the effects of diet on this study's results are unknown. In addition, no attempt was made to control for reproductive history or for developmental conditions that might relate to susceptibility to metabolic disease (e.g. Barker, 1997). While it might be possible to add reproductive and developmental data for these subjects retrospectively, subsequent analysis would require further breaking down the samples according to parity, birth weight, or other factors. This would only exacerbate the potential issues with statistical power. Instead, future research that incorporates data on development and reproductive history, as well as attempts to control or at least assess diet, can perhaps better isolate and evaluate the effects of exercise on postmenopausal metabolic function.

Conclusions

This study addressed the broad question: do high levels of exercise promote the maintenance of basic metabolic function, even in the face of the hormonal changes associated with menopause? Limited to the small sample presented here,

the answer appears to be no, for both habitual, moderate exercise and for the exercise intervention in sedentary postmenopausal women. On the other hand, when compared to the physical activity level and body composition of highly trained postmenopausal athletes (e.g. Van Pelt et al., 1997) and hunter-gatherers, this study's subjects were not particularly active, and had body fat percentage consistent with risk for developing metabolic and cardiovascular disease. These findings are consistent with the existence of a threshold effect for the intensity of exercise. Moreover, considering that exercise tends to elicit changes in body composition and metabolic health in younger women, the absence of an effect of exercise imposed after menopause indicates that the timing of establishing exercise habits relative to menopause is also important. Thus, the question should be modified in part to ask: *how much* exercise promotes the maintenance of postmenopausal metabolic function? Moreover, it is critical to gain a better understanding of the pattern of age-related decline in the physiological response to exercise, and how that decline affects the potential of exercise to improve metabolic health after menopause.

These revised questions can be addressed by future research that evaluates more precisely how, when and why the musculoskeletal and metabolic responses to exercise decline with age. If additional factors such as diet, early developmental experiences, and reproductive history might also influence postmenopausal metabolic physiology, then their interaction with the effects with exercise should be investigated too. As highly active individuals who rarely experience the metabolic and constitutional changes associated with menopause in industrialized societies, hunter-gatherer women may provide the best data with which to test and formulate new hypotheses about exercise and healthy aging. Limited as it is, the currently available

postmenopausal hunter-gatherer dataset shows promising results, and should expand as a focus of future research.

Evolutionary hypotheses and comparative data provide an understanding of how our species' physiology has been shaped over time, and how genes interact with environment and behavior to determine phenotypic expression. Studying variation in phenotypic expression from an evolutionary perspective, especially when phenotypes appear abnormal or maladaptive, compels researchers to evaluate not only the underlying proximate, physiological causes of disease, but to also seek the larger, evolutionary conditions that have shaped physiological systems. In the case of postmenopausal metabolic physiology, low levels of estradiol-17β may correlate with changes in body composition and REE, but a broader interpretation might suggest that the hyposteroidal environment is only a disease risk factor when the absence of vigorous physical activity has disjoined an individual's physiology from the conditions under which it evolved. Continued application of the principles of evolutionary medicine to the study of the postmenopausal life history period can guide researchers toward better paths for disease prevention, and ideally improve the conditions of postmenopausal life for a great many women.

APPENDIX

The following abbreviations for variables are used in the tables and figures below:

BIA:	bioelectrical impedance analysis
DXA:	dual-energy x-ray absorptiometry
Fat%:	body fat percentage
FFM:	fat-free mass
FM:	fat mass
Hip circ.:	hip circumference
PAL:	physical activity level
REE:	resting energy expenditure
$\dot{V}O_{2MAX}$:	maximal aerobic capacity
Waist circ.:	waist circumference

Table A.1: Age at natural menopause in different populations*

Population	N	Mean ± SD	Median	Reference
Argentina: urban	2,100	---	48.9	Blümel et al. (2006)
Australia	650		50.4	Walsh (1978)
Bangladesh: rural	2,324	---	43.6	Karim et al. (1985)
Bolivia: rural	125	42.3 ± 6.2	---	Castelo-Branco et al. (2005)
Bolivia: urban	1,750	---	47.9	Blümel et al. (2006)
Botswana: rural (!Kung)	33	---	49.1	Hunt and Newcomer (1984)
Brazil: urban	350	---	51.2	Blümel et al. (2006)
Chile: urban	1,750	---	49.6	Blümel et al. (2006)
China: urban	1,011	48.9 ± 3.1	---	Ku et al. (2004)
Colombia: urban	700	---	51.4	Blümel et al. (2006)
Costa Rica: urban	350	---	50.3	Blümel et al. (2006)
Cuba: urban	350	---	50.2	Blümel et al. (2006)
Ecuador: urban	1,400	---	48.6	Blümel et al. (2006)
Finland: urban/rural	1,505	51.7	51.0	Luoto et al. (1994)
Germany	2,097	---	51.1	Fuchs and Paskarbeit (1976)
Ghana: urban	123	48.1 ± 3.6	48.0	Kwawukume et al. (1993)
India: urban/rural	201	46.7 ± 4.2	48.0	Kriplani and Banerjee (2005)
India: rural	65	47.5 ± 3.7	---	Kapoor and Kapoor (1986)
Indonesia: urban	346	---	50.5	Samil and Wishnuwardhani (1994)
Iran: urban/rural	8,194	50.4 ± 4.3	49.6	Mohammad et al. (2004)
Iran: urban	948	48.3 ± 5.3	49.0	Ayatollahi et al. (2003)
Japan: rural	1,513	49.6 ± 3.3	---	Kono et al. (1990)
Japan: urban	4,964	49.8 ± 3.2	---	Kono et al. (1990)
Lebanon: urban	298	---	49.3	Reynolds and Obermeyer (2001)
Malaysia: urban	400	---	50.7	Ismael (1994)
Mexico: urban	472	46.5 ± 5.0	47.0	Garrido-Latorre et al. (1996)
Morrocco: urban	299	---	48.4	Reynolds and Obermeyer (2003)
Nepal: rural	52	45.9 ± 5.7	46.8	Beall (1983)
Netherlands	8,064	---	51.4	sources in McKinlay et al. (1985)
New Zealand	485	---	50.7	Burch and Gunz (1967)
Nigeria: urban	676	49.4 ± 5.0	---	Adekunle et al. (2000)
Nigeria: urban/rural	563	48.4 ± 5.0	48.0	Okofonua et al. (1990)
Panama: urban	350	---	51.2	Blümel et al. (2006)

*Age at menopause in years via recall interview, defined as one year since last menses.

Table A.1 (continued): Age at natural menopause in different populations*

Population	N	Mean ± SD	Median	Reference
PNG: rural	?	---	47.3	Scragg (1973)
Paraguay: urban	1,050	---	47.5	Blümel et al. (2006)
Peru: urban	640	---	47.10	Gonzalez et al. (1997)
Philippines: urban	500	---	48.0	Ramoso-Jalbuena (1994)
Russia: urban	1,939	49.0 ± 5.0	---	Balan (1995)
Saudi Arabia: urban	391	48.9 ± 5.7	50.0	Greer et al. (2003)
Singapore: urban	495	49.1 ± 3.9	---	Chim et al. (2002)
Slovakia: urban/rural	6,877	51.2 ± 4.4	---	Magurský et al. (1975)
South Africa: rural	1,850	49.5 ± 4.7	---	Walker et al. (1984)
South Africa: urban	1,255	48.9 ± 4.2	---	Walker et al. (1984)
South Korea: urban	961	49.3 ± 3.5	---	Ku et al. (2004)
Sweden: urban	?	---	50.9	Hagstad (1988)
Switzerland: urban	381	49.8 ± 4.2	50.0	Morabia et al. (1996)
Taiwan: urban/rural	386	49.5 ± 2.3	---	Chow et al. (1997)
Thailand: urban	100	50.3 ± 3.8	---	Tungphaisal et al. (1991)
Turkey: urban	1,516	47.8 ± 4.0	51.0	Carda et al. (1998)
UAE: urban/rural	742	47.3 ± 3.3	48.0	Rizk et al. (1998)
UK	962	---	50.6	sources in McKinlay et al. (1985)
USA: urban	15,785	---	51.3	Kato et al. (1998)
Yap: rural	436	---	48.6	Hunt and Newcomer (1984)

*Age at menopause in years via recall interview, defined as one year since last menses.

Table A.2: This study's sample characteristics at baseline

	Pooled (N=41)	Active (N=19)	Training (N=18)
Age (years)	60.4 ± 1.1 (48-79)	61.8 ± 1.5 (49-72)	59.5 ± 1.8 (48-79)
REE (kcal/d)****	1250 ± 26 (951-1531)	1278 ± 35 (998-1526)	1191 ± 36 (951-1513)
Weight (kg)	64.4 ± 1.7 (43.8-84.9)	64.7 ± 2.5 (43.8-84.1)	63.9 ± 2.4 (46.3-84.9)
Height (cm)	165 ± 1.3 (151-185)	164 ± 2.1 (152-185)	165 ± 1.8 (151-177)
Waist circ. (cm)	81.3 ± 1.4 (64.3-103.0)	81.6 ± 2.1 (64.3-103.0)	80.4 ± 1.9 (67.2-98.1)
Hip circ. (cm)	99.2 ± 1.3 (86.6-114.7)	98.7 ± 2.0 (87.4-114.7)	100.0 ± 2.0 (86.6-113.0)
FFM_{DXA} (kg)	42.8 ± 0.9 (31.1-59.1)	44.1 ± 1.5 (33.6-59.1)	41.1 ± 1.2 (31.1-51.7)
FFM_{BIA} (kg)	42.3 ± 0.8 (32.0-55.3)	43.0 ± 1.2 (35.5-55.3)	41.3 ± 1.2 (32.0-53.7)
$FFM_{4\text{-SKINFOLDS}}$ (kg)	39.7 ± 0.9 (27.3-51.7)	40.3 ± 1.3 (32.5-51.7)	38.6 ± 1.3 (27.3-50.8)
$FFM_{7\text{-SKINFOLDS}}$ (kg)	46.9 ± 1.1 (33.2-61.3)	47.1 ± 1.6 (38.2-60.8)	45.9 ± 1.5 (33.2-61.3)
FM_{DXA} (kg)	21.7 ± 1.0 (10.0-35.1)	20.6 ± 1.5 (10.0-31.9)	22.8 ± 1.4 (14.8-33.2)
FM_{BIA} (kg)	22.1 ± 1.2 (7.1-36.4)	21.7 ± 1.8 (7.1-36.4)	22.6 ± 1.7 (13.4-36.0)
$FM_{4\text{-SKINFOLDS}}$ (kg)	24.7 ± 0.9 (9.4-36.1)	24.5 ± 1.5 (9.4-36.1)	25.2 ± 1.3 (14.8-34.1)
$FM_{7\text{-SKINFOLDS}}$ (kg)	17.5 ± 0.8 (5.5-29.6)	17.6 ± 1.4 (5.5-29.6)	17.9 ± 1.1 (8.8-24.5)
$Fat\%_{DXA}$**	33.1 ± 0.9 (23-42)	31.2 ± 1.4 (23-41)	35.2 ± 1.1 (29-42)
$Fat\%_{BIA}$	33.6 ± 1.1 (16-46)	32.6 ± 1.8 (16-44)	34.7 ± 1.5 (22-46)
$Fat\%_{4\text{-SKINFOLDS}}$	38.0 ± 0.8 (22-46)	37.3 ± 1.3 (22-46)	39.2 ± 0.9 (29-43)
$Fat\%_{7\text{-SKINFOLDS}}$	26.8 ± 0.8 (13-37)	26.7 ± 1.4 (13-37)	27.8 ± 0.9 (17-32)
$\dot{V}O_{2MAX}$ (ml O_2/kg/min)***	23.3 ± 1.0 (12.9-35.8)	27.3 ± 1.4 (17.8-35.8)	19.6 ± 1.0 (12.9-26.5)
PAL (xREE)***	1.16 ± 0.02 (1.01-1.49)	1.25 ± 0.02 (1.08-1.49)	1.05 ± 0.01 (1.01-1.24)

*Reported as mean ± SEM (range)

**Active and Training groups differ significantly, independent samples t-test (p <0.05).

***Active and Training groups differ significantly, independent samples t-test (p <0.01).

****Difference between Active and Training groups approaches significance (p =0.09).

Table A.3: Correlations between variables at baseline in the Pooled sample

	REE	Weight	Height	FFM_{DXA}	FM_{DXA}	$Fat\%_{DXA}$	$\dot{V}O_{2MAX}$	PAL
Age	r = -0.427**	r = -0.267	r = -0.332*	r = -0.264	r_s = -0.210	r_s = -0.104	r_s = 0.003	r_s = 0.251
REE		r = 0.693**	r = 0.504**	r = 0.735**	r_s = 0.488**	r_s = 0.179	r_s = 0.076	r_s = 0.240
Weight			r = 0.576**	r = 0.838**	r_s = 0.886**	r_s = 0.555**	r_s = -0.311	r_s = -0.134
Height				r = 0.707**	r_s = 0.351*	r_s = 0.003	r_s = 0.049	r_s = -0.078
FFM_{DXA}					r_s = 0.520**	r_s = 0.031	r_s = 0.073	r_s = 0.144
FM_{DXA}						r_s = 0.851**	r_s = -0.567**	r_s = -0.359*
$Fat\%_{DXA}$							r_s = -0.774**	r_s = -0.546**
$\dot{V}O_{2MAX}$								r_s = 0.636**

r-values are Pearson's product-moment correlation; r_s-values are Spearman's rank-order coefficient.

*$p \leq 0.05$

**$p \leq 0.01$

Table A.4: Correlations between variables at baseline in the Active sample

	REE	Weight	Height	FFM_{DXA}	FM_{DXA}	$Fat\%_{DXA}$	$\dot{V}O_{2MAX}$	PAL
Age	r = -0.494*	r = -0.214	r = -0.212	r = -0.244	r = -0.123	r_s = -0.067	r = -0.173	r = 0.147
REE		r = 0.868**	r = 0.659**	r = 0.882**	r = 0.617**	r_s = 0.250	r = -0.121	r = 0.249
Weight			r = 0.443*	r = 0.838**	r = 0.858**	r_s = 0.578**	r = -0.476*	r = 0.024
Height				r = 0.704**	r = 0.068	r_s = -0.103	r = 0.106	r = 0.271
FFM_{DXA}					r = 0.439*	r_s = 0.009	r = -0.089	r = 0.291
FM_{DXA}						r_s = 0.822**	r = -0.708**	r = -0.234
$Fat\%_{DXA}$							r_s = -0.752**	r_s = -0.446*
$\dot{V}O_{2MAX}$								r = 0.458*

Coefficients: r-values are Pearson's product-moment correlation; r_s-values are Spearman's rank-order coefficient.

*$p \leq 0.05$

**$p \leq 0.01$

Table A.5: Correlations between variables at baseline in the Training sample

	REE	Weight	Height	FFM_{DXA}	FM_{DXA}	$Fat\%_{DXA}$	$\dot{V}O_{2MAX}$	PAL
Age	r = -0.575*	r = -0.425	r = -0.466*	r = -0.482*	r = -0.310	r_s = -0.115	r = -0.264	r_s = 0.344
REE		r = 0.628*	r = 0.473*	r = 0.562*	r = 0.594**	r_s = 0.389	r = 0.063	r_s = 0.024
Weight			r = 0.745**	r = 0.913**	r = 0.931**	r_s = 0.629**	r = -0.198	r_s = -0.111
Height				r = 0.852**	r = 0.540*	r_s = -0.013	r = 0.031	r_s = 0.000
FFM_{DXA}					r = 0.701**	r_s = 0.173	r = 0.034	r_s = -0.038
FM_{DXA}						r_s = 0.812**	r = -0.377	r_s = -0.142
$Fat\%_{DXA}$							r_s = -0.540*	r_s = -0.331
$\dot{V}O_{2MAX}$								r_s = 0.326

Coefficients: r-values are Pearson's product-moment correlation; r_s-values are Spearman's rank-order coefficient.

*$p \leq 0.05$

**$p \leq 0.01$

Table A.6: Repeated measures linear mixed models results*

	Group	Baseline	Week 5	Week 10	Week 16
REE (kcal/d)***,d	Active	1278 ± 35	1283 ± 37	1283 ± 33	1277 ± 34
	Training	1191 ± 36	1251 ± 38	1205 ± 31	1192 ± 36
Weight (kg)[d]	Active	64.7 ± 2.5	64.2 ± 2.6	64.0 ± 2.6	64.1 ± 2.6
	Training	63.9 ± 2.4	63.9 ± 2.1	64.0 ± 2.3	63.7 ± 2.3
Height (cm)[d]	Active	164.0 ± 2.1	163.8 ± 2.0	163.9 ± 2.0	163.8 ± 2.0
	Training	164.6 ± 1.8	164.5 ± 1.8	164.7 ± 1.8	164.8 ± 1.8
Waist circ. (cm)[b]	Active	81.6 ± 2.1	83.3 ± 2.6	80.9 ± 2.2	80.6 ± 2.1
	Training	80.4 ± 1.9	79.9 ± 2.0	78.9 ± 2.0	79.0 ± 1.8
Hip circ. (cm)[d]	Active	98.7 ± 2.0	97.3 ± 2.1	97.3 ± 2.1	98.4 ± 1.8
	Training	100.0 ± 2.0	100.0 ± 1.9	100.3 ± 1.9	99.8 ± 1.9
FFM_{DXA} (kg)[d]	Active	44.1 ± 1.5	---	---	44.1 ± 1.6
	Training	41.1 ± 1.2	---	---	41.2 ± 1.2
FFM_{BIA} (kg)[d]	Active	43.0 ± 1.2	42.4 ± 1.2	42.6 ± 1.2	42.7 ± 1.2
	Training	41.3 ± 1.2	41.7 ± 1.1	41.8 ± 1.1	42.0 ± 1.2
$FFM_{4\text{-SKINFOLDS}}$ (kg)[d]	Active	40.2 ± 1.3	40.7 ± 1.4	40.9 ± 1.4	40.9 ± 1.4
	Training	38.6 ± 1.3	38.5 ± 1.2	38.6 ± 1.2	38.5 ± 1.2
$FFM_{7\text{-SKINFOLDS}}$ (kg)[d]	Active	47.1 ± 1.6	47.9 ± 1.7	47.9 ± 1.7	48.3 ± 1.7
	Training	45.9 ± 1.5	45.9 ± 1.4	46.1 ± 1.5	45.9 ± 1.4
FM_{DXA} (kg)[b]	Active	20.6 ± 1.5	---	---	20.0 ± 1.5
	Training	22.8 ± 1.4	---	---	22.5 ± 1.3
FM_{BIA} (kg)[d]	Active	21.7 ± 1.8	21.8 ± 1.8	21.4 ± 1.7	21.4 ± 1.8
	Training	22.6 ± 1.7	22.1 ± 1.5	22.1 ± 1.5	21.7 ± 1.3
$FM_{4\text{-SKINFOLDS}}$ (kg)[b,c]	Active	24.5 ± 1.5	23.5 ± 1.5	23.1 ± 1.4	23.2 ± 1.5
	Training	25.2 ± 1.3	25.3 ± 1.3	25.4 ± 1.3	25.2 ± 1.2
$FM_{7\text{-SKINFOLDS}}$ (kg)[b,c]	Active	17.6 ± 1.4	16.3 ± 1.3	16.1 ± 1.2	15.8 ± 1.1
	Training	17.9 ± 1.1	18.0 ± 1.1	17.9 ± 1.1	17.8 ± 1.0

* Reported as mean ± SEM.

** Groups significantly different at baseline, $p<0.05$.

*** Groups approaching significant difference at baseline, $p<0.10$.

a. Group main effect significant, overall F-test $p<0.05$.

b. Time main effect significant, overall F-test $p<0.05$.

c. Group x time interaction significant, overall F-test $p<0.05$.

d. No significant effects of group, time, or group x time, overall F-test.

Table A.6 (continued): Repeated measures linear mixed models results*

	Group	Baseline	Week 5	Week 10	Week 16
$Fat\%_{DXA}$**,a	Active	31.2 ± 1.4	---	---	30.6 ± 1.3
	Training	35.2 ± 1.1	---	---	34.9 ± 1.0
$Fat\%_{BIA}$d	Active	32.6 ± 1.8	33.1 ± 1.7	32.5 ± 1.6	32.6 ± 1.6
	Training	34.7 ± 1.5	34.1 ± 1.2	34.0 ± 1.2	33.7 ± 1.0
$Fat\%_{4\text{-}SKINFOLDS}$a,b,c	Active	37.3 ± 1.3	36.1 ± 1.4	35.6 ± 1.2	35.7 ± 1.2
	Training	39.2 ± 0.9	39.4 ± 0.8	39.4 ± 0.8	39.3 ± 0.8
$Fat\%_{7\text{-}SKINFOLDS}$b,c	Active	26.7 ± 1.4	24.9 ± 1.3	24.7 ± 1.2	24.2 ± 1.0
	Training	27.8 ± 0.9	27.8 ± 1.0	27.6 ± 1.0	27.7 ± 0.9
$\dot{V}O_{2MAX}$	Active	27.3 ± 1.4	---	---	27.9 ± 1.5
(ml O_2/kg/min)**,a,b	Training	19.6 ± 1.0	---	---	21.3 ± 1.0

* Reported as mean ± SEM.

** Groups significantly different at baseline, $p<0.05$.

*** Groups approaching significant difference at baseline, $p<0.10$.

a. Group main effect significant, overall F-test $p<0.05$.

b. Time main effect significant, overall F-test $p<0.05$.

c. Group x time interaction significant, overall F-test $p<0.05$.

d. No significant effects of group, time, or group x time, overall F-test.

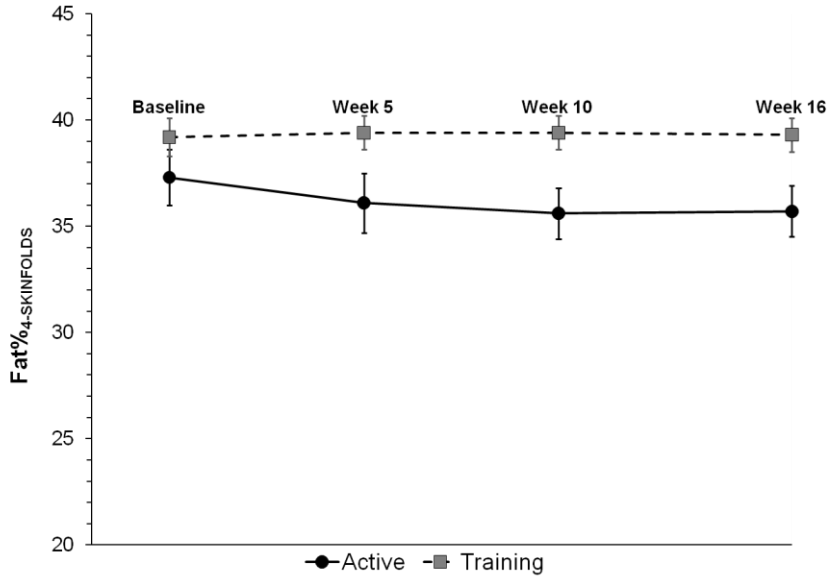

Figure A.1: Fat%$_{4\text{-SKINFOLDS}}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.04; time p=0.05; group x time p=0.01.

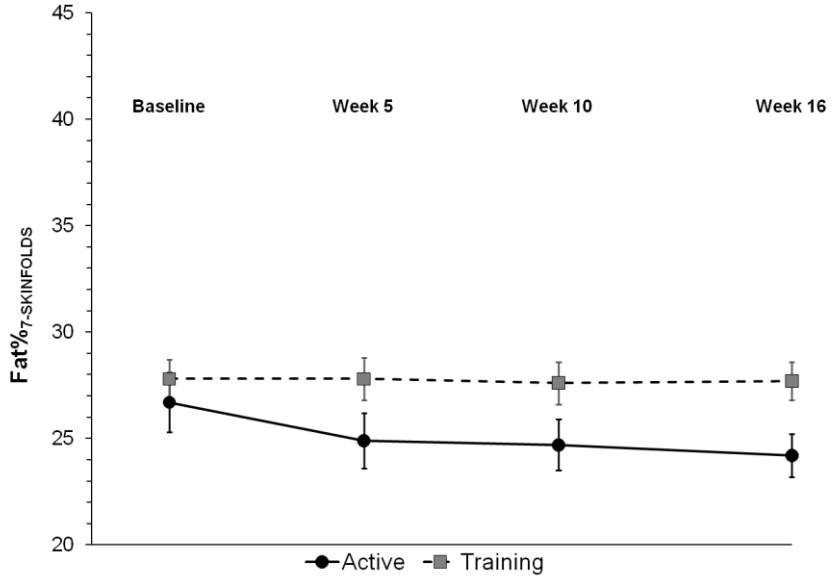

Figure A.2: Fat%$_{7\text{-SKINFOLDS}}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.10; time p=0.01; group x time p=0.02.

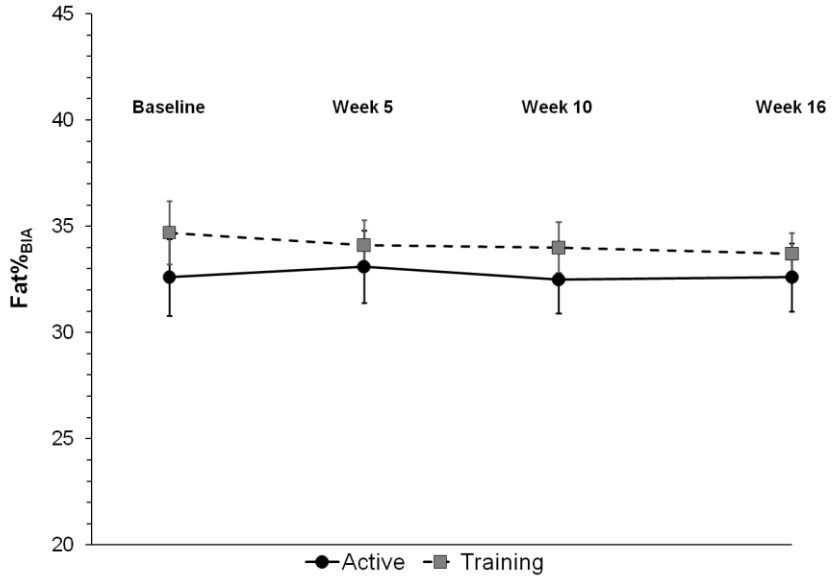

Figure A.3: Fat%$_{BIA}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.49; time p=0.51; group x time p=0.49.

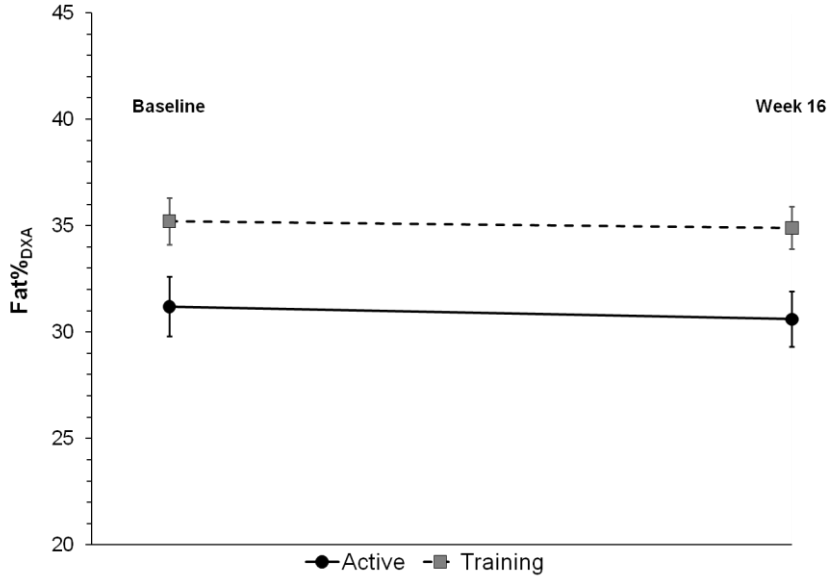

Figure A.4: Fat%$_{DXA}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.02; time p=0.08; group x time p=0.42.

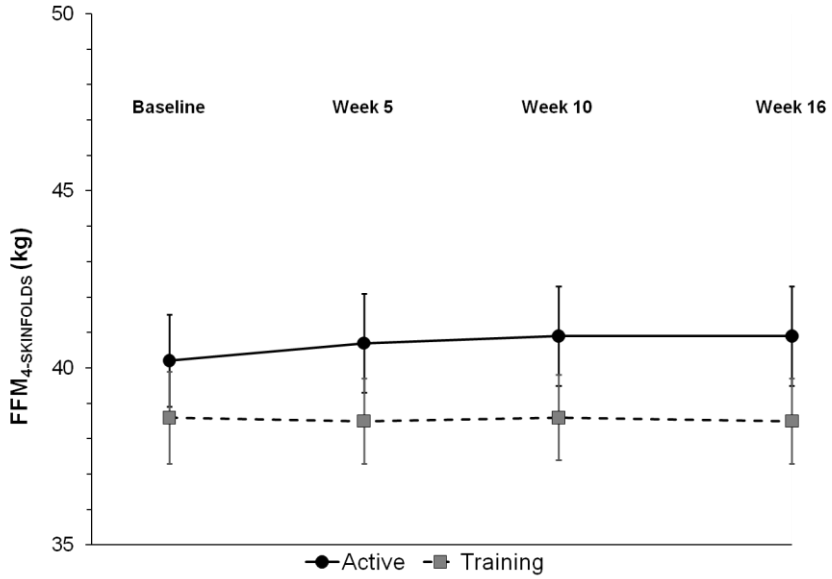

Figure A.5: $FFM_{4\text{-}SKINFOLDS}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.26; time p=0.51; group x time p=0.27.

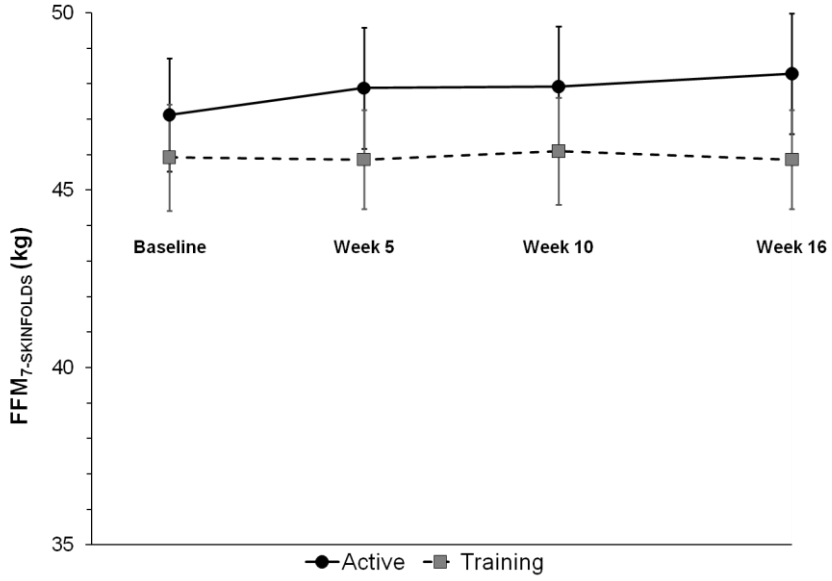

Figure A.6: $FFM_{7\text{-}SKINFOLDS}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.41; time p=0.12; group x time p=0.08.

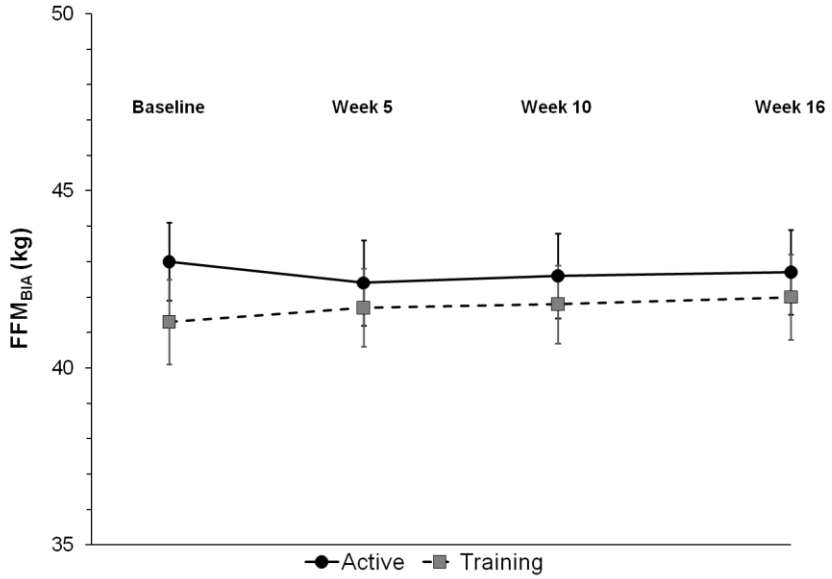

Figure A.7: FFM_{BIA} within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.56; time p=0.77; group x time p=0.16.

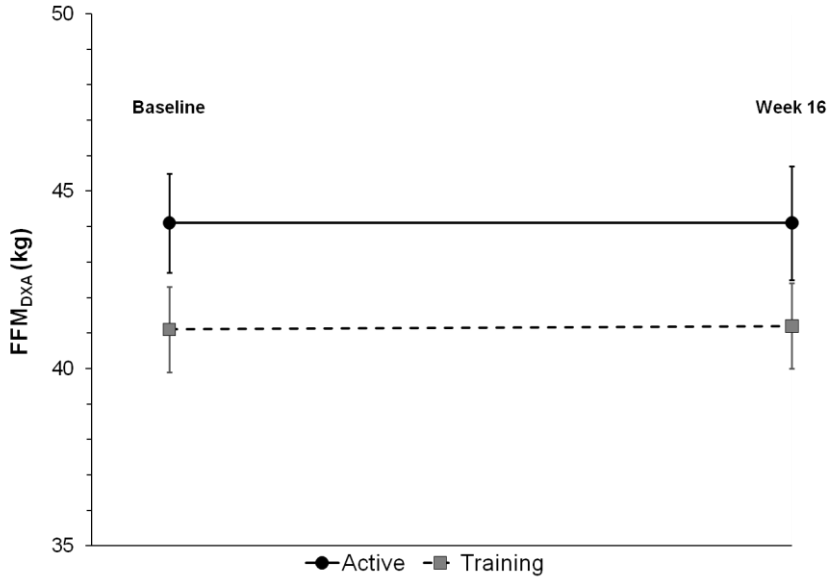

Figure A.8: FFM_{DXA} within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.13; time p=0.71; group x time p=0.63.

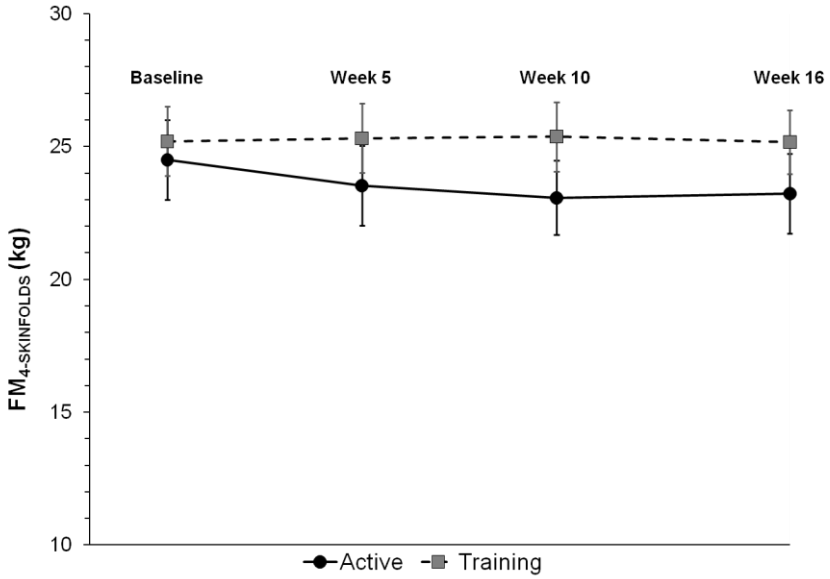

Figure A.9: $FM_{4\text{-SKINFOLDS}}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.39; time p=0.01; group x time p<0.01.

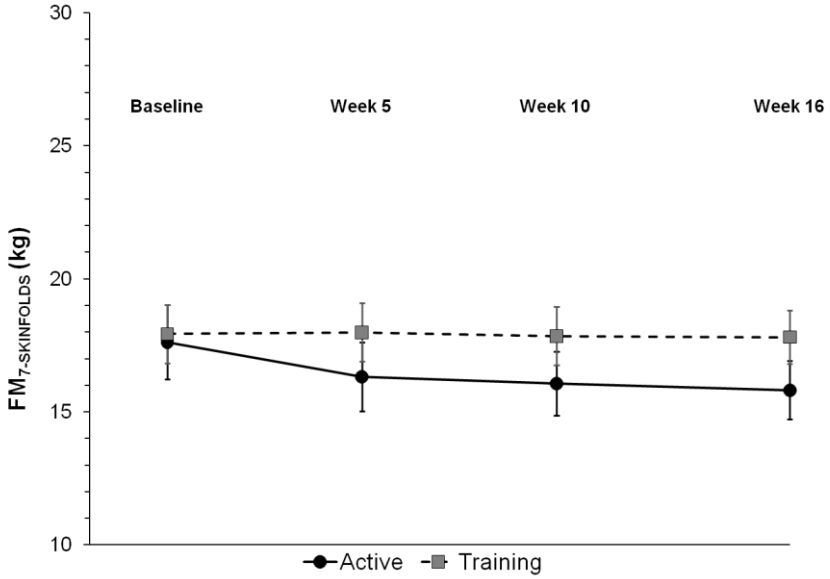

Figure A.10: $FM_{7\text{-SKINFOLDS}}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.38; time p<0.01; group x time p<0.01.

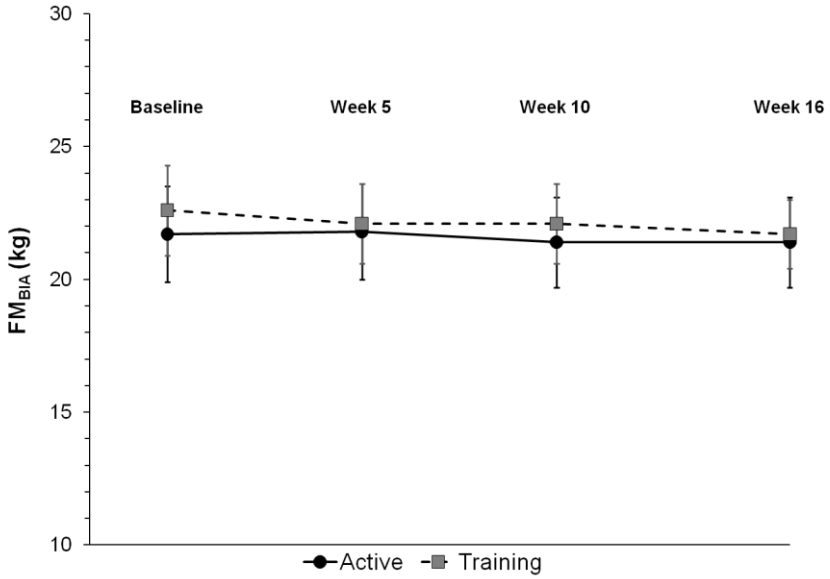

Figure A.11: FM_{BIA} within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.82; time p=0.22; group x time p=0.70.

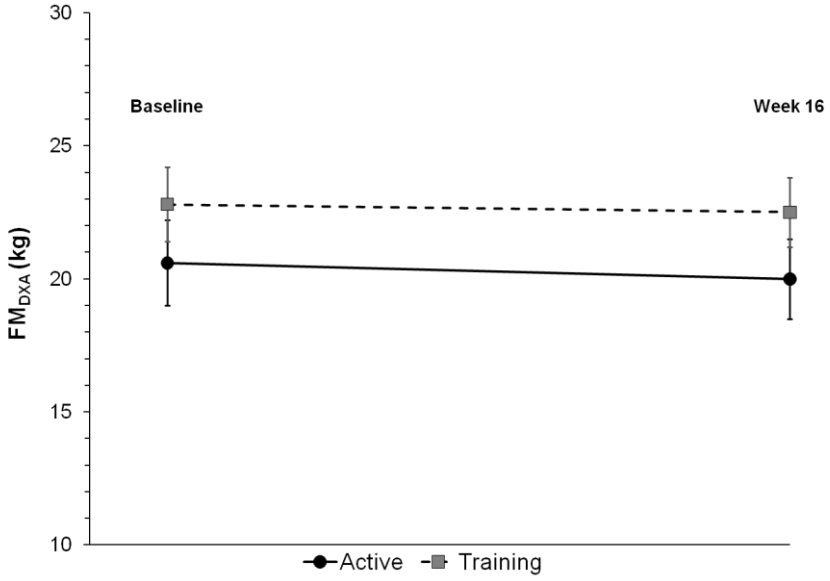

Figure A.12: FM_{DXA} within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.25; time p=0.02; group x time p=0.40.

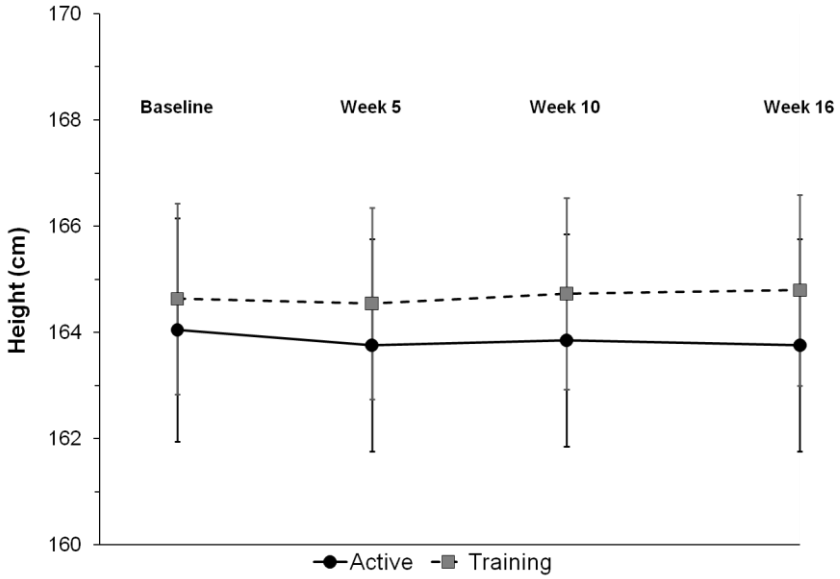

Figure A.13: Height within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.77; time p=0.29; group x time p=0.17.

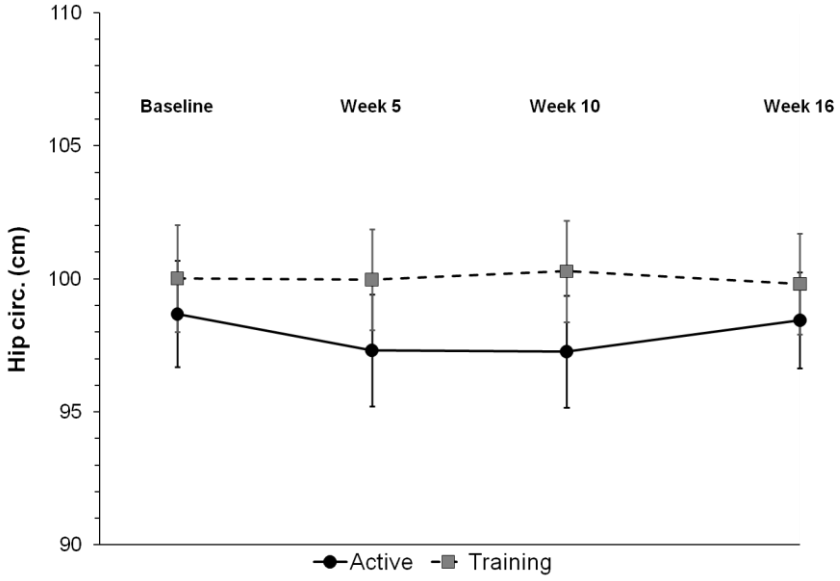

Figure A.14: Hip circumference within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.45; time p=0.58; group x time p=0.34.

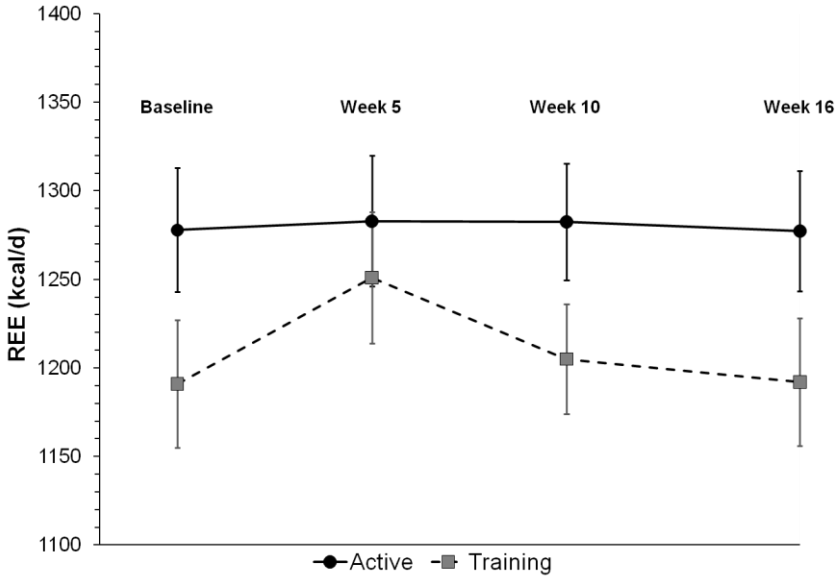

Figure A.15: REE within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.11; time p=0.27; group x time p=0.40.

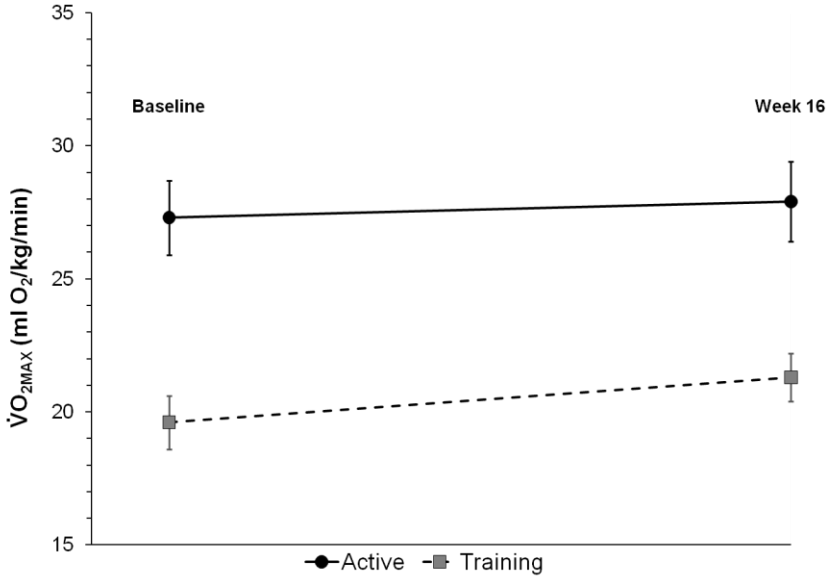

Figure A.16: $\dot{V}O_{2MAX}$ within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p<0.01; time p=0.02; group x time p=0.46.

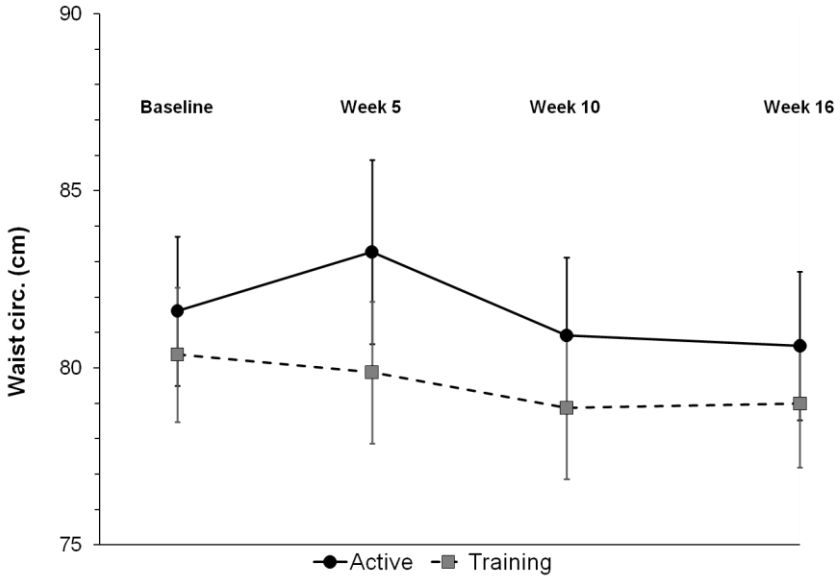

Figure A.17: Waist circumference within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.47; time p=0.03; group x time p=0.41.

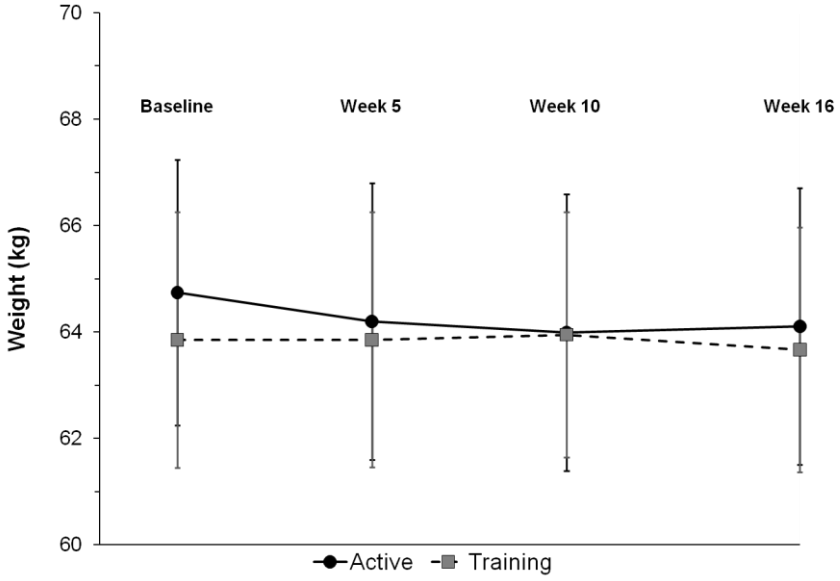

Figure A.18: Weight within groups at each testing period

Notes: Circles/squares represent means, error bars denote SEM. Repeated measures fixed effects: group p=0.90; time p=0.10; group x time p=0.10.

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