Published in final edited form as:

Sports Med. 2011 January 1; 41(1): 73–86. doi:10.2165/11536860-000000000-00000.

Sex Hormone Effects on Physical Activity Levels: Why Doesn't Jane Run as Much as Dick?

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Abstract

The relationship between physical activity levels and disease rates have become an important health related concern in the developed world. Heart disease, certain cancers, and obesity persist at epidemic rates in the United States and Western Europe. Increased physical activity levels have been shown to reduce the occurrence of many chronic diseases leading to reductions in the burden on the health care system. Activity levels in humans are affected by many cultural and environmental factors, nevertheless current research points to a strong biological input with potential genetic, neurological, and endocrinological origins. Of unique interest, the sex hormones appear to have a very strong influence on activity levels. The current animal literature suggests that females tend to be more active than males due to biological pathways of estrogenic origin. The majority of human epidemiological and anthropological data, on the contrary, suggest women are less active than men in spite of this inherent activity-increasing mechanism. The purpose of this manuscript was to review the current literature regarding the control of physical activity levels by the sex hormones in humans. Using the natural transitional phases of the aging endocrine system, natural periodicity of the menstrual cycle, and pharmacological/hormone replacement therapy as variable experimental stages, some authors have been able to provide some information regarding the existence of an inherent activity-increasing mechanism in humans. In brief, activity levels during life stages prior to and after menopause do not significantly differ, despite the vast changes in sex hormone levels and function. Activity difference throughout a regular menstrual cycle do not appear to influence activity levels in humans either—an effect that is pronounced in the female rodent. The use of hormone replacement therapies provide researchers with more systematic controls over hormone modulation in human subjects; however, this benefit comes with additional confounding variables, mostly due to disease or other states of malfunction. Despite the addition of these confounding factors, minor changes to the activity pattern have been observed in women, especially during the initial administration for the therapy. Observations are yet to be made in male subjects during replacement therapy. In general, some evidence exists suggesting that a biological mechanism—extending from the sex hormones—influences activity in humans. Unfortunately, despite a small number of investigative reports, the paucity of human research investigating how the sex hormones affect activity levels in humans prevents conclusive delineation of the mechanisms involved. Future research in this unique sub-field of endocrinology and exercise science utilizing more appropriate research protocols and effective techniques will provide definitive evidence of such mechanisms.

It is axiomatic that the daily accumulation of physical activity will offset many different health conditions and will lead to increased quality and quantity of life. However, there are stark differences in the amount of regular physical activity that human males and females complete with little scientific explanation for these differences. While the regulation of

physical activity has long been thought of as voluntary and/or influenced solely by environmental factors, there is a growing body of evidence that suggests that physical activity, as defined as movement that is not forced upon the individual, is at least partially regulated by biological factors [1-11]. These biological regulating factors may take many forms including an increase or decrease of various physiological substance or structures, and/or genetics which may fundamentally alter receptor/protein interaction in the intact organism [6,7,9]. While beyond the scope of this review, extensive animal literature has shown that sex of the individual significantly influences physical activity patterns by working through various sex-related hormonal pathways [12]. Biologically, sex hormones play a large role in regulating various physiological parameters; thus, they have naturally been the subjects of investigations trying to elucidate the possible roles they play in regulating physical activity in animals. However, at this point the role that sex hormones play in regulating human activity has been largely unexplored, probably due to the unappreciated role that biological factors play in regulating 'voluntary' activity. The increasing rate of cardiovascular and other hypokinetic diseases in women [13] make understanding the mechanisms regulating physical activity in human females critical in the context of the health-related goals of our society. Thus, the focus of this paper is to review the literature investigating the effect of and the possible physiological mechanisms through which the various sex hormones regulate physical activity in humans.

For the purpose of this review, physical activity level will be considered the total amount of activity an individual accomplishes in the course of a day which not only includes formal exercise, but movement that is associated with activities of daily living (e.g. stair climbing, yard work, etc.). This operational definition includes estimates of physical activity level based on energy expenditure levels that are corrected for body mass. Whereas males of most species generally have larger masses than females, presenting energy expenditure data as physical activity levels without correcting for mass biases the estimates toward males regardless of total daily activity.

The literature for this review was identified using standard literary search techniques. The PubMed database was searched across all years covered within the database using multiple search terms including: sex or gender difference, sex steroids, sex hormones, physical activity, activity, physical activity levels, locomotion, or exercise. The uncovered literature was then evaluated and only studies investigating the effects of sex on activity in which activity was treated as the dependent variable were accepted for review. Furthermore, articles investigating the extrinsic and/or environmental influences on activity were not included in the present review. Thus, the current review focused on the effects sex has on physical activity levels in humans and was not intended to be an exhaustive review of the regulatory mechanism underlying general physical activity levels in humans.

1. Brief Overview of the Biochemistry of Sex Hormones

The biochemistry of sex hormones is well understood and summarized in Figure 1. Sex hormones primarily consist of androgens (testosterone) and estrogens (estradiol). Both are primarily derived from progestins (progesterone) or from pregnenolone via dehydroepiandrosterone, androstenedione, and androstenediol, which are formed from cholesterol upon stimulation by adrenocorticotrophic hormone (ACTH). While the primary sex hormones differ between males (testosterone) and females (estrogen) as do the primary sites of synthesis (testes – male; ovaries – female), quantities of testosterone and estrogen occur in both sexes. Testosterone is also an intermediate substance in the formation of estrogen in both males and females. Through an aromatization process using the aromatase enzyme complex, testosterone is converted to 17 β -estradiol; this conversion is not reversible. In males, while some testosterone is converted to estrogen, the majority of

testosterone is converted into dihydrotestosterone, which cannot be aromatized into estrogen. While testosterone concentration exhibits minor variations on a daily basis in healthy, adult males ($\approx 6\text{--}10\text{ ng}\cdot\text{ml}^{-1}$), estrogen and progesterone exhibit cyclical peaks in females, with estrogen peaking at approximately $200\text{--}300\text{ pg}\cdot\text{ml}^{-1}$ at day 12 of the menstrual cycle (during the *follicular* phase) then drops to approximately $100\text{--}150\text{ pg}\cdot\text{ml}^{-1}$ during the early *luteal*/late *follicular* transition. A progesterone peak of $8\text{--}10\text{ ng}\cdot\text{ml}^{-1}$ occurs at approximately day 20 of the cycle and is coupled with a concurrent rise in estrogen to approximately $150\text{--}200\text{ pg}\cdot\text{ml}^{-1}$ (during the *luteal* phase). The hormonal fluctuations evident in females are characteristic of healthy, adult females and are not typically seen in pre-pubescent girls or menopausal women.

2. Do the Sex Hormones regulate Physical Activity Levels in Humans?

The available animal literature (see reference [12] for a current review) strongly suggests the presence of a physical activity regulating mechanism centered around sex hormone physiology. In rodents, wheel running is reduced after surgical/pharmacological gonadectomy and is increased after hormones are reintroduced via capsules or injections. The necessary ethical limitations of human subjects research have limited the use of such experimental manipulations in humans leading to a reduced understanding of the biological mechanisms present in humans contributing to physical activity regulations. Through use of natural (due to sex, aging and the menstrual cycle) and artificial changes in clinical populations (pharmacological and hormone replacement therapies), some research has been compiled to evaluate the extent to which sex hormones regulate activity in the human population.

2.1 Are females and males differentially active?

If sex hormones play a role in the regulation of daily activity patterns, it is appropriate to hypothesize that male and female activity patterns would differ, especially given the cyclical nature of sex hormones in females. The extensive animal literature [12] shows that female rodents, in general, are more active on a daily basis than male rodents, regardless of the measurement used. Interestingly, the majority of literature investigating this question in humans shows that human females, whether child, adolescent, or adult, are less active on a daily basis than males. Pate and colleagues, in an extensive review of physical activity in adolescents showed that female children and adolescents were generally less active than males [14]. This trend continues into adulthood; Figure 2 represents findings from the 2001 [15,16] and 2007 [17] United States Behavioral Risk Factor Surveillance Survey (BRFSS). In 2001, over 200,000 individuals were surveyed and showed that a greater percentage of males met physical activity recommendations for moderate and/or vigorous exercise than did adult females—the 2001 survey was limited to exercise activity, and thus was limited in its ability to identify energy expenditure extending from tasks of daily living. The 2007 dataset was expanded to include over 400,000 subjects and additional questions were added to better identify activities of daily living habits. The 2007 survey identified an even larger activity gap between the sexes in normal weight, overweight, and obese adults. Recent accelerometer data (Figure 2) from Troiano et al. [18] from the 2003-04 National Health and Nutrition Examination Survey (NHANES) shows the same qualitative pattern—males were slightly more active than females—but as compared to the BRFSS data, shows a significantly lower number of individuals that actually complete moderate activity. The same male-female differential activity pattern has also been observed in the non-technical Old Order Amish culture [19] as well as in several hunter/gatherer cultures (Figure 3 - the Nuñoa and Tamang being notable exceptions) indicating that in general, regardless of culture, males are more active than females [20,21]. Therefore, in contrast to the well-established rodent literature, the majority of the available literature suggests that human males are more active than human females [12]. The causes of differential activity levels in

humans are not entirely known; however, measurement of activity levels surrounding naturally or artificially induced changes in sex hormone concentrations may enhance our understanding of the sexually differentiated activity pattern.

2.2 Is there a difference between activity levels before and after menopause?

The transition in female humans at menopause allows activity to be compared under two very different hormonal conditions. Prior to menopause, the sex hormones circulate in higher concentrations compared to the concentrations experienced after menopause. Unfortunately, the scientific literature has yet to address this question directly or in sufficient detail. In one indirect study, Dorn et al. [22] investigated breast cancer risk in pre- and post-menopausal women with and without breast cancer. As a component of this analysis, the researchers asked the subjects to recall their strenuous physical activity patterns during the previous two years. Due to their illness, the patients with breast cancer likely had activity patterns that were deviant from normal and therefore were not considered for this review. Unfortunately, statistical comparisons were not made between the two control groups to directly evaluate pre- and post-menopause activity levels; however, these subjects estimated their yearly strenuous physical activity to be 77.3 ± 127.8 h·yr⁻¹ in women prior to menopause and 68.4 ± 176.7 h·yr⁻¹ in women after menopause [22]. While it is tempting to infer a reduction in activity after the decline in hormone concentration after menopause, the considerable variation in the activity measurement and the varying ages of the subjects significantly complicates this comparison. Thus, while the literature is limited, the use of both cross-sectional and longitudinal studies measuring activity levels pre- and post-menopause is certainly warranted.

2.3 Does physical activity change across the menstrual cycle?

Examination of activity patterns in eumenorrheic women provides a hormonal concentration milieu that is unique. Tworoger and colleagues [23] reported the results of a carefully crafted correlational study that used data from 565 pre-menopausal women, ages 33-52 years, which were originally surveyed in the Nurses' Health Study II. The investigators measured a wide-variety of sex hormones in blood samples taken during the luteal and follicular phases of the menstrual cycle in woman that varied in amount of physical activity preformed during a typical week as gathered through self-report questionnaires. These authors noted that while in general there were no strong associations between physical activity and testosterone, progesterone, or follicular estradiol levels, there was an inverse association ($p=0.05$) between activity and luteal estrogen levels. Unfortunately, interpretation of any relationship between activity levels and estrogen levels in this study is difficult because body fat levels were lower in those women that were more active. Given that adipose tissue can increase estrogen levels [24], the lower body fat levels of the active women could have confounded the negative relationship between activity levels and estrogen levels in this study.

2.4 Do hormone replacement therapies or pharmacological interventions alter activity levels?

Females—As noted earlier, there is extensive rodent literature suggesting that estrogen in particular, but also testosterone [12], increases activity levels via activation of the estrogen alpha-receptor pathway leading to downstream regulation of other physiological structures, potentially in the brain. While limited data exists to answer whether this is also true in humans, the studies that have been done have addressed the effect of hormone replacement therapy (HRT) on physical activity in women. Using a correlational design, Andersen et al. [25] observed that in the NHANES III data, women who had never used HRT reported higher levels of inactivity (40%) as compared to those women who had used HRT (28.5%)

suggesting that women who had not used HRT (decreased estrogen) were more likely to be sedentary (decreased activity) when compared to those women that had used HRT. While supporting the hypothesis of sex hormone effects on activity levels, a major limitation of the NHANES III data was that it surveyed leisure time activity alone without regard for activities of daily living. Thus, any women that did not report any leisure time activity were classified as sedentary/inactive in spite of potential vigorous activity completed as part of their daily lives. Another research design issue with this data was the lack of control for the type of HRT or delivery method used (e.g. oral or transdermal; see below for further consideration).

Redberg et al. [26] stratified 248 post-menopausal women based on their HRT use and interviewed them regarding their physical activity, with physical activity levels estimated as Mets·h/wk (Figure 4A). The physical activity data were analyzed across four different groups (each subject was included in one or more of the experimental groups): those women currently on HRT (n=108) versus those not currently on HRT (n=140) and those women who were currently or had been on HRT (n=158) versus those who had never used HRT (n=90). Ninety four percent of the HRT subjects (n=101) used oral estrogen therapy while transdermal estrogen was used in six percent of the subjects (n=7). Of the group currently using HRT, 48% were on combined estrogen/progestin supplementation with the composition of the HRT for the remainder of the subjects not noted. Redberg and colleagues [26] reported large variability in physical activity in each group (Figure 4A) with no significant differences between any of the groups, thus concluding that activity was not affected by HRT status.

Anderson et al. [27] conducted a repeated measures trial on younger (45-55 yrs, n=18) post-menopausal and older (70-80 yrs, n=15) post-menopausal women investigating the effect of transdermally applied estrogen and estrogen plus vaginally-applied progesterone supplementation on a variety of energy balance measures with a two month washout between treatments. This study was unique in that the estrogen and progesterone treatments were carefully titrated to result in near physiological circulating levels of both estrogen (76.89 ± 4.43 - 80.50 ± 5.43 pg·ml⁻¹) and progesterone (7.09 ± 0.91 ng·ml⁻¹). Furthermore, the subjects were encouraged not to lose weight while in the experimental program. Figure 4B shows that Anderson and colleagues [27] observed no differences in physical activity level as measured by survey techniques across the treatments, thus supporting the lack of an effect of HRT on activity levels.

Kenny and colleagues [28] completed a three-year double blind, placebo-controlled trial investigating the effect of estrogen therapy on various muscle and physical functions in 167 older (average age at baseline $\approx$ 74 yrs) post-menopausal women. The women were randomly assigned to either an estrogen treatment group (0.25 mg oral 17 β -estradiol) or a placebo group (Figure 4C). Physical activity was estimated at the beginning of the study and then once per year for the three year trial using the Physical Activity Scale in the Elderly (PASE). Kenny et al. [28] reported that while the baseline activity scores were different between the groups, the rate of decrease in activity during the three years was the same in all of the groups.

Poehlman et al. [29] published a purported six-year controlled longitudinal study of HRT and energy balance that supposedly showed an increase in leisure time activity with HRT. Unfortunately, this article was subsequently retracted from the literature when the author admitted to fabricating the data in the study [30-32].

Males—In males, two possible avenues could be used to artificially manipulate sex hormone levels in order to evaluate effects on activity. In one approach, the effects of

antiandrogens (e.g. flutamide)—often prescribed for individuals at risk of or suffering from prostate cancer, as well as those suffering from a severe sexual disorder—on activity could be considered. However, there have been no published investigations on the effects of antiandrogens on physical activity. A second avenue would be to consider the effects of suprapharmacological doses of androgens on activity. While there are anecdotal statements of hyperactivity in individuals taking suprapharmacological doses of androgens [33] there have been no studies that directly or indirectly measured physical activity levels in these subjects and possible changes with androgen supplementation.

There is a large body of literature concerning aggression with androgen supplementation in both men and women. Unfortunately, using the data on androgen supplementation and aggression to infer possible linkages between androgen supplementation and physical activity levels is difficult due to the possible confounding effects of the various psychological states occurring with suprapharmacological doses of androgens and the uncertainty regarding gonadal sufficiency of the subjects.

The human data available regarding the sex hormone effects on activity are sparse and that which exists only addresses female subjects. While the female correlational data are split, with one study showing a positive relationship between lack of HRT and inactivity [25] and one showing no relationship [23], all of the available prospective studies [26-28] do not support the contention that estrogen administration alters physical activity. These studies are strong from the standpoint that in each case, total daily physical activity levels were estimated as opposed to estimation of just leisure time activities as was the case with the NHANES III data [25]. However, definitive conclusions are difficult to reach due to several possible confounding research design factors.

3. Are Research Design Issues the Reason for Species Differences in Sex Hormone Effects in Rodents and Humans?

Animals, especially rodents, have been used to model phenotypes or physiological phenomenon in humans with reasonable success. However, as has been discussed, the animal data show conclusively that sex hormones—specifically estrogen—exert powerful effects on daily activity, while the limited human data suggests that sex hormones play no role in the biological regulation of activity. Thus, the species difference in sex hormone effects on activity requires the consideration of several factors including 1) appropriateness of the animal model, 2) how dependency is assigned to variables, 3) whether rodent modes of activity directly translate to the measurement of activity in humans, and 4) how the hormones are replaced or introduced to the organism. These factors help to outline the limitations of animal to human translation in physical activity level research and provide a foundation for future investigations in both humans and animal models.

3.1 Appropriateness of rodents as models of human physiology

Any consideration of species differences, especially differences between rodents and human models, must begin with questioning the appropriateness of using rodents to investigate human health questions. A variety of scientific organizations recognize the usefulness of rodents in modeling human physiology, especially with less than 1% of the mouse genome differing significantly from the human genome [34]. Specifically, rodents are used frequently as models of human sex hormone physiology; in 2006 and 2007, the National Library of Medicine listed 881 articles that were published concerning mice and reproductive hormones. For example, rodent models have been used extensively to document the role of estrogen α and β -receptors ($ER\alpha$ and $ER\beta$) in human cardiovascular physiology [35]. It is reasonable to suggest that biological data collected in rodents can be

applied to human physiology; however, the multifactorial nature of human behavioral traits complicates the translation between species.

Environmental factors affect human and rodent behavioral traits differently; therefore, the extension of results from rodents to humans requires extensive caution. Evidence of an animal decision-making capacity based on a free will directive is limited, but the existence of such a mechanism in humans may impose extensive complexity on the outward expression of a behavioral trait. The decision to be physically active or physically inactive may invariably result from decisions made in response to the free will input, thus the lack of a free will directive in animals may explain the differences in volume of activity performed between high activity rodents and low active humans. However, the existence of free will is insufficient to explain why an apparent bias exists between human males and females—it is difficult to impute that a sex bias affects free will directives in humans; that is to say, that one sex is more proficient at utilizing or abiding by their free will directive. A more likely explanation is that extrinsic variables—free will included—are subject to pressures exerted by biological inputs, which may override the effects of the extrinsic stimuli.

Role dynamics and societal structure may also influence behavior characteristics in humans differently than rodents. In the study, by Bassett et al. [19] variability in the amount of activity performed between the sexes may be explained by the volume or the workload the typical male and female-associated tasks required. Males performed more labor-intensive activities in this cultural group and thus the appearance of the male activity bias is a byproduct of societal workload expectancies rather than the sex hormones. Uniquely, however, a bias for higher activity levels in males exists in indigenous people groups known to follow societal organizational principles quite different from Western society. The Ju/'hoansi exhibit a similar male activity bias observed in Western cultures, but follow egalitarian principles [36]. The male bias is not present in the overall activity levels of the egalitarian Tamang population; however, corrections for basal metabolic rate or activity intensity—outdoor subsistence activities elevate energy demand compared indoor activities and lead to a higher energy expenditure in the individuals performing the outdoor activities—instill a male bias in this population [21].

Clearly, human complexity—extending from cultural, environmental, and emotional stimuli—is an important consideration when detailing the effectiveness of an animal model to represent behavioral traits in humans. From the perspective of physical activity, it appears that the effects of these extrinsic factors are likely limited. Furthermore, the increasing rate of physical inactivity in the US despite a plethora of literature examining the effects of extrinsic factors on human activity levels provide additional impetus that the biological regulation of activity levels remain of intransient importance. Indeed, differences exist between the modeled and actual response, but the discrepancies in the animal and available human literature may exist because of methodological rather than model representation issues.

3.2 Independent versus dependent variables

Another factor that confounds the determination of whether sex hormones play a causative role in the regulation of daily activity in humans is experimental design issues, especially the assignment of independent/dependent variable relationships. While the animal literature has primarily studied the effect of sex hormones (i.e. independent variable) on physical activity (i.e. dependent variable), the majority of research in the human literature has approached physical activity as the independent variable, with sex hormone levels treated as dependent variables. This approach is somewhat understandable given the belief that activity levels were controlled by voluntary directives and not the product of biological factors and thus, could not be affected by biological manipulation. With mounting evidence that ‘voluntary’

physical activity levels may actually be driven to a significant extent by biological/genetic factors [6,7,9,37], it becomes important to understand the factors—such as sex hormones—that regulate daily activity. The understanding that there are discrete biological/genetic factors that drive ‘voluntary’ physical activity calls for further carefully controlled studies—in addition to the three studies currently available [26-28]—where activity level is the *dependent variable* with hormone level/supplementation as the *independent variable*. This approach would allow further understanding in the human model of the role of sex hormones—much as has been done in the animal literature.

3.3 Use of surveys to determine physical activity

The use of surveys or questionnaires to estimate physical activity levels in all of the current human studies limits conclusions. Numerous reviews (e.g. ref. [38]) have observed that survey estimations of physical activity generally overestimate actual activity levels. This was reinforced recently by Troiano and colleagues [18] when they measured daily activity in a large population using accelerometers and found only a small percentage ($3.5 \pm 0.3\%$) of adults completed moderate activity on a daily basis as compared to other survey estimates of adult activity levels (e.g. $45.4 \pm 0.2\%$, ref. [15]). As noted in an extensive review of the reliability, validity, and sensitivity of physical activity questionnaires [38], correlation coefficients between measurement of physical activity (e.g. doubly-labeled water or accelerometers) and questionnaire results vary widely with few rising above 0.60 and with the questionnaires generally overestimating activity levels. Specifically, two factors that often lead to the least valid estimates of activity are the length of time separating the recall from the activity and individuals whom have lower levels of activity [38]. It is difficult to determine the possible effect of these two confounding factors on the conclusions of the currently available prospective HRT studies [27,28] given that none listed the recall period that was used in their studies even though the instruments used by Kenny et al. [28] and Anderson et al. [27] were designed to estimate daily activity based on a seven day recall period. Therefore, to eliminate the possible confounds of using survey/questionnaire approaches which grossly overestimate daily activity, the use of direct measures of activity, such as was done in the NHANES 03-04 study [18] would considerably strengthen the investigation of sex hormone effects on daily activity levels.

3.4 Mode of hormone therapy used

The method of hormone delivery can significantly influence the circulating concentrations of sex hormone [39]. For example, plasma concentrations of orally delivered hormone reaches peak physiological levels approximately three hours after administration and then declines rapidly [39] exposing the individual to a non-physiological pattern of sex hormone concentration over the course of a 24 hour period. The use of transdermal administration provides a more stable plasma concentration of hormone, but to this point, only one of the prospective studies [27] used transdermal administration and verified constant, physiological concentrations of the sex hormones in their subjects.

Additionally, other than the Anderson et al. [27] study, no study has delineated the type of estrogen/progesterone used in prospectively assessing the effect of sex hormones on activity. Both the ER α and ER β preferentially bind to certain estrogenic substrates. As noted earlier, the estrogen α -receptor pathway has been shown to be the primary pathway involved in physical activity regulation. With different estrogens and progestins used in common HRT formulations [39] and the hypothesized activity inducing actions of the estrogen- α pathway [12], it is possible that different HRT formulations produce different physical activity responses solely due to the lack of a compound with the necessary ability to bind to the estrogen- α receptor.

Thus, while the limited human data suggests that female activity patterns are not influenced by sex hormones, given the methodological limitations present, this conclusion is tentative at best and misleading at worst. Future studies controlling type and concentration of hormone replacement, the use of research designs that recognize that activity levels are influenced by biological factors, and the direct measurement of daily activity will provide further information to support or refute this hypothesis. However, while extremely speculative, if we assume that the current human data are representative of the human activity response to sex hormones, the question of why there is a species difference in the activity patterns of female rodents versus humans remains enigmatic.

4. Summary and Conclusions

There is no doubt that increasing physical activity levels in adult populations, both nationally and internationally, should be a health-related priority and the fact that general levels of physical activity in both adults and children are less than optimal (e.g. refs. [14,18]) is troubling. Decades of activity promotion and research have not produced a noticeable reduction in the number of inactive individuals. Thus, these data present a clarion call for a greater understanding of the underlying mechanisms regulating voluntary daily activity and the roles that biological/genetic factors play in activity regulation. The plethora of epidemiological evidence that suggests that human females, in most cases, are less active than males, along with increasing rates of cardiovascular disease in women [13], provides additional impetus for understanding all factors involved in activity regulation. In spite of the strong animal literature that suggests a probable physiological mechanism of activity regulation by sex hormones [12], human females are still generally less active than males. Thus, the question becomes and remains as to whether the environmental/cultural influences on physical activity override the increased physical activity drive inherent in women.

While there is some literature suggesting differential environmental, cultural, and psychological effects on activity levels between the sexes, there is no literature available investigating the interaction of these factors and biological effects on activity. Further study is warranted that specifically sets hormone concentration as an independent variable. Ideally, experimental modulation of hormone levels in a wider variety of individuals is necessary to completely understand the influence hormone levels have on activity. Such studies should capitalize on current therapeutic intervention used by medical professionals to manage endocrine related diseases and disorders including birth control administration, testosterone treatments, and hormone replacement therapy. The naturally occurring variation of hormone levels in both males and females throughout the life cycle, during distinct physiological conditions such as the luteal and follicular phases of the menstrual cycle, and between individuals may also add appropriate and measurable variability that allows independence to be assigned to hormone concentration. Additionally, the more reliable estimation of activity achieved through use of accelerometers and other quantifiable forms of locomotion measurement should be utilized in place of traditional survey methods.

The clinical implications of expanding this research are potentially far reaching. Currently, a large body of literature exists regarding how extrinsic and environmental factors influence physical activity levels in humans, unfortunately beneficial alterations to health indicators are minimal and physical inactivity and related conditions remain disproportionately high. Thus, physical activity management strategies and research agendas that focus solely on environmental or extrinsic factors remains shortsighted. The overall goal of physical activity-sex hormone interaction research should be to further delineate biological pathways and identify enzymes/proteins/biomolecules involved in up-regulating activity levels in humans. In doing so, the medical community may in fact find ways in which to capitalize on

these biomolecules and pathways leading to promotion of physical activity and increased beneficial health outcomes in the general population.

Acknowledgments

The authors would like to thank the editing and proofreading comments of the Kinesiology Writing Accountability Klatch: Drs. T. Hubbard, S. Tsivitse, and M. Cordova, as well as suggestions for studies and verbiage to include in this review by A. M. Knab. This review supported by funding from NIH NIAMS RO1AR050085.

References

1. Festing MF. Wheel activity in 26 strains of mouse. *Lab Anim* Oct;1977 11(4):257–8. [PubMed: 926756]
2. Joosen AM, Gielen M, Vlietinck R, et al. Genetic analysis of physical activity in twins. *Am J Clin Nutr* Dec;2005 82(6):1253–9. [PubMed: 16332658]
3. Kaprio, J.; Koskenvuo, M.; Sarna, S. *Prog Clin Biol Res*. Alan R Liss; New York (NY): 1981. Cigarette smoking, use of alcohol, and leisure-time physical activity among same-sexed adult male twins. *Twin research 3: epidemiological and clinical studies*; p. 37-46.
4. Lauderdale DS, Fabsitz R, Meyer JM, et al. Familial determinants of moderate and intense physical activity: a twin study. *Med Sci Sports Exerc* Aug;1997 29(8):1062–8. [PubMed: 9268964]
5. Lerman I, Harrison BC, Freeman K, et al. Genetic variability in forced and voluntary endurance exercise performance in seven inbred mouse strains. *J Appl Physiol* Jun;2002 92(6):2245–55. [PubMed: 12015333]
6. Lightfoot JT, Turner MJ, Daves M, et al. Genetic influence on daily wheel running activity level. *Physiol Genomics* Nov 17;2004 19(3):270–6. [PubMed: 15383638]
7. Lightfoot JT, Turner MJ, Pomp D, et al. Quantitative trait loci for physical activity traits in mice. *Physiol Genomics* Feb 19;2008 32(3):401–8. [PubMed: 18171721]
8. Perusse L, Tremblay A, Leblanc C, et al. Genetic and environmental influences on level of habitual physical activity and exercise participation. *Am J Epidemiol* May;1989 129(5):1012–22. [PubMed: 2705422]
9. Stubbe JH, Boomsma DI, De Geus EJ. Sports participation during adolescence: a shift from environmental to genetic factors. *Med Sci Sports Exerc* Apr;2005 37(4):563–70. [PubMed: 15809553]
10. Stubbe JH, Boomsma DI, Vink JM, et al. Genetic influences on exercise participation in 37,051 twin pairs from seven countries. *PLoS One* 2006;1:e22. [PubMed: 17183649]
11. Turner MJ, Kleeberger SR, Lightfoot JT. Influence of genetic background on daily running-wheel activity differs with aging. *Physiol Genomics* Jun 16;2005 22(1):76–85. [PubMed: 15855385]
12. Lightfoot JT. Sex hormones' regulation of rodent physical activity: a review. *Int J Biol Sci* 2008;4(3):126–32. [PubMed: 18449357]
13. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol* Nov 27;2007 50(22):2128–32. [PubMed: 18036449]
14. Pate RR, Long BJ, Heath G. Descriptive epidemiology of physical activity in adolescents. *Pediatr Exerc Sci* 1994;6(4):434–47.
15. Macera CA, Ham SA, Yore MM, et al. Prevalence of physical activity in the United States: Behavioral Risk Factor Surveillance System, 2001. *Prev Chronic Dis* Apr;2005 2(2):A17. [PubMed: 15888228]
16. McCracken M, Jiles R, Blanck HM. Health behaviors of the young adult U.S. population: Behavioral Risk Factor Surveillance System, 2003. *Prev Chronic Dis* Apr;2007 4(2):A25. [PubMed: 17362616]
17. Prevalence of self-reported physically active adults--United States, 2007. *MMWR Morb Mortal Wkly Rep* Dec 5;2008 57(48):1297–300. [PubMed: 19052527]
18. Troiano RP, Berrigan D, Dodd KW, et al. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc* Jan;2008 40(1):181–8. [PubMed: 18091006]

19. Bassett DR, Schneider PL, Huntington GE. Physical activity in an Old Order Amish community. *Med Sci Sports Exerc* Jan;2004 36(1):79–85. [PubMed: 14707772]
20. Leslie PW, Bindon JR, Baker PT. Caloric requirements of human populations: a model. *Hum Ecol* 1984;12(2):137–62.
21. Panter-Brick C. Seasonal and sex variation in physical activity levels among agro-pastoralists in Nepal. *Am J Phys Anthropol* May;1996 100(1):7–21. [PubMed: 8859950]
22. Dorn J, Vena J, Brasure J, et al. Lifetime physical activity and breast cancer risk in pre- and postmenopausal women. *Med Sci Sports Exerc* Feb;2003 35(2):278–85. [PubMed: 12569217]
23. Tworoger SS, Missmer SA, Eliassen AH, et al. Physical activity and inactivity in relation to sex hormone, prolactin, and insulin-like growth factor concentrations in premenopausal women - exercise and premenopausal hormones. *Cancer Causes Control* Sep;2007 18(7):743–52. [PubMed: 17549594]
24. Yang K, Khalil MW, Strutt BJ, et al. 11 Beta-Hydroxysteroid Dehydrogenase 1 activity and gene expression in human adipose stromal cells: effect on aromatase activity. *J Steroid Biochem Mol Biol* Feb;1997 60(3-4):247–53. [PubMed: 9191983]
25. Andersen RE, Crespo CJ, Franckowiak SC, et al. Leisure-time activity among older U.S. women in relation to hormone-replacement-therapy initiation. *J Aging Phys Act* 2003;11(1):82–9.
26. Redberg RF, Nishino M, McElhinney DB, et al. Long-term estrogen replacement therapy is associated with improved exercise capacity in postmenopausal women without known coronary artery disease. *Am Heart J* Apr;2000 139(4):739–44. [PubMed: 10740161]
27. Anderson EJ, Lavoie HB, Strauss CC, et al. Body composition and energy balance: lack of effect of short-term hormone replacement in postmenopausal women. *Metabolism* Mar;2001 50(3):265–9. [PubMed: 11230776]
28. Kenny AM, Kleppinger A, Wang Y, et al. Effects of ultra-low-dose estrogen therapy on muscle and physical function in older women. *J Am Geriatr Soc* Nov;2005 53(11):1973–7. [PubMed: 16274381]
29. Poehlman ET, Toth MJ, Gardner AW. Changes in energy balance and body composition at menopause: a controlled longitudinal study. *Ann Intern Med* Nov 1;1995 123(9):673–5. [PubMed: 7574222]
30. Sox HC. Notice of retraction: final resolution. *Ann Intern Med* May 3;2005 142(9):798. [PubMed: 15845952]
31. Poehlman ET. Notice of retraction: final resolution. *Ann Intern Med* May 3;2005 142(9):798. [PubMed: 15845951]
32. Sox HC. Notice of retraction. *Ann Intern Med* Oct 21;2003 139(8):702. [PubMed: 14568863]
33. Salvador A, Moya-Albiol L, Martinez-Sanchis S, et al. Lack of effects of anabolic-androgenic steroids on locomotor activity in intact male mice. *Percept Mot Skills* Feb;1999 88(1):319–28. [PubMed: 10214660]
34. Waterston RH, Lindblad-Toh K, Birney E, et al. Initial sequencing and comparative analysis of the mouse genome. *Nature* Dec 5;2002 420(6915):520–62. [PubMed: 12466850]
35. Arias-Loza PA, Jazbutyte V, Fritzemeier KH, et al. Functional effects and molecular mechanisms of subtype-selective ERalpha and ERbeta agonists in the cardiovascular system. *Ernst Schering Found Symp Proc* 2006;(1):87–106. [PubMed: 17824173]
36. Lee, R. *The Dobe Ju/'Hoansi (case studies in cultural anthropology)*. 3rd ed.. Wadsworth Publishing; Belmont, CA: 2003.
37. Simonen RL, Rankinen T, Perusse L, et al. Genome-wide linkage scan for physical activity levels in the Quebec Family study. *Med Sci Sports Exerc* Aug;2003 35(8):1355–9. [PubMed: 12900690]
38. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med* Jun;2003 37(3):197–206. [PubMed: 12782543]
39. Turgeon JL, Carr MC, Maki PM, et al. Complex actions of sex steroids in adipose tissue, the cardiovascular system, and brain: Insights from basic science and clinical studies. *Endocr Rev* Oct;2006 27(6):575–605. [PubMed: 16763155]

Figure 1. Basic pathways for sex hormone biochemistry in mammalian species. Double-headed arrows represent reversible reactions; single-headed arrows represent one-way reactions. The general sex hormone classes are grouped in dashed boxes.

Figure 2.

Percentage of U.S. adults meeting moderate/vigorous activity recommendations. Males are the hatched bars and females are the open bars. The total data included all subjects, overweight data included subjects with a BMI between 25.0 and 29.9 kg/m², and obese data included subjects with a BMI $\geq$ 30.0 kg/m². Data redrawn from United States 2001 [15,16] and 2007 [17] Behavioral Risk Factor Surveillance Survey (BRFSS) and the 2003-2004 [18] National Health and Nutrition Examination Survey (NHANES). BRFSS data are presented as the whole dataset [15,17] and subdivided by weight status [16].

Figure 3.

Hours per day of moderate-vigorous activity in Hunter/Gatherer cultures. Males are the hatched bars and females are the open bars. Data for the Nuñoa, Kaul, Lufa, and Ju/'hoansi populations are redrawn from Leslie et al. [20] and data for the Tamang population are redrawn from Panter-Brick [21]. Note: The Ju/'hoansi people are referred to as !Kung in the manuscript [20] in which these data were taken. This terminology refers to the language spoken by the Ju/'hoansi peoples and is now considered offensive and derogatory [36].

Figure 4.

The effect of hormone replacement therapy (HRT) on physical activity. Panel A represents the lack of difference in physical activity estimates amongst any of the HRT and non-HRT groups and represents tabular data from Redberg et al. [26]. Panel B shows the lack of an effect of HRT, both estrogen (E₂) and estrogen plus progesterone (E₂ + P) treatments, on estimated activity levels in younger menopausal and older menopausal subjects. Data taken from Anderson et al. [27]. Panel C represents the lack of a difference in estimated physical activity between low-dose estrogen and placebo over a 36-month period. *indicates a significant difference from placebo treatment at same time period. Data taken from Kenny et al. [28].

Figure 5. Hypothesized avenues of biological regulation resulting in differential controls of physical activity in male and female humans. Double-headed arrows indicate potential two-way influences.