Physical activity and depressive symptoms

Stavrakakis, Nikolaos

Publication date:
2015

CHAPTER I

General Introduction

"Mens sana in corpore sano"
(A healthy mind existing in a healthy body)

Juvenal, *Satire X*

GENERAL INTRODUCTION

Physical activity (PA) is considered to be beneficial to general health. However, the benefits of PA on mental health, and especially depression are less clear. This thesis explores in depth the relationship between PA and depressive symptoms, in adolescents and adults.

Definition of Physical Activity and Depression

It is important to clarify some of the terms that will be used in this thesis, namely, PA, physical fitness (PF)[1], exercise, sports and depression.

Physical Activity, Physical Fitness, Exercise and Sports

The main two distinctive groups are PA and PF, while exercise and sports are subgroups of PA. PF is defined as "the ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies" (Caspersen et al., 1985; see p. 128). Hence, PF reflects health attributes (for example, cardiovascular endurance, muscular endurance and strength, flexibility), as well as skills related to athletic ability (accuracy, spatio-temporal coordination, etc.). PA is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al., 1985; see p. 126). The energy expenditure is commonly measured in kilocalories (kcal) or kilojoules (kJ). PA can be classified in many different ways. The simplest way to classify PA is by distinguishing between activity while working and activity during leisure-time (voluntary activity)[2]. Further classifications include light, moderate, and intensive activities, team activities, and outdoor activities. The intensity of each activity can be expressed in the Metabolic Equivalent of Tasks (MET). The MET score assesses the energy cost of PA and is defined as "the ratio of the associated metabolic rate for the specific activity divided by the resting metabolic rate (RMR)[3]" (Ainsworth et al., 1993; see page 72)[4].

Although PA and exercise share common characteristics and have been used interchangeably in the literature, exercise is a distinct subcomponent of PA. Exercise is defined as "any physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is (the) objective" (Caspersen et al., 1985; see page 128). The term 'sports' does not have a universal definition, but the majority of definitions on what constitutes a sport tend to converge on a competitive element. The Oxford dictionary defines sport as: "an activity involving physical exertion and skill in which an individual or team competes against another or others for entertainment"[5]. Thus, the term 'sports' is also a subcomponent of PA and shares common traits with exercise.

Depression

Depression has been defined in diverse ways in the literature (Abela & Hankin, 2008) and is considered a largely heterogeneous disorder (Hasler, Drevets, Manji, & Charney, 2004; Lux & Kendler, 2010). Generally, depression is characterized as a state of low mood or a loss of interest, which affects an individual's well-being, cognition and behavior (Joorman, 2009). According to DSM-V criteria for major depressive disorder (MDD), at least one of the symptoms of depressed mood and loss of interest or pleasure has to be present for 2 weeks. At least five of the following nine additional symptoms should also persist almost every day for at least 2 weeks: a) appetite problems, that is, weight loss or weight gain, or decrease or increase in appetite; b) sleep difficulties, such as hyper-insomnia or insomnia; c) fatigue or loss of energy; d) feelings of worthlessness; e) psychomotor agitation; f) cognitive problems, such as diminished ability to concentrate and indecisiveness; and g) suicidal ideation or suicide attempts (American Psychiatric Association, 2013). The prevalence rates of MDD are higher than of all other psychiatric disorders, with approximately 19% of the Dutch population experiencing a clinically significant episode at least once in their lives[6] (de Graaf, ten Have, van Gool, & van Dorsselaer, 2012).

Humans Evolved to Move

PA has been at the core of every free-living organism's evolutionary history. The relationship between caloric acquisition (energy consumed as food) and caloric expenditure, i.e., PA, has exerted an "ongoing adaptive pressure that affected (the) selection of genes related to the cardio-respiratory and musculoskeletal systems as well as the internal metabolism processes of our progenitors" (Eaton & Eaton, 2003; see p. 153). This can be seen in the evolution of the human species, where the environmental pressures that have acted in order to produce our unique human nature have taken place immediately after the 'split' between our pre-human ancestors with those of the modern day apes (pongids), an estimated 5-7 million years ago (Cordain et al., 1998; Eaton & Konner, 1985). The appearance of the *Australopithecines*[7], approx. 4 million years ago[8] coincided with gradual environmental changes in the African continent, which resulted in a 'drying' up of tropical forests to a more open savanna (Behrensmeyer & Cooke, 1985; deMonocal & Bloemendal, 1995; Foley, 1987). The early hominins developed specific structural and functional characteristics, which helped them exploit their changing environment in ways that their pongid ancestors could not (see for example: Leonard & Robertson, 1997). The first such change was the ability to walk straight (bipedalism[9]), which was still relatively primitive compared to the abilities of (much) later hominins (i.e., *Homo habilis*, *Homo erectus* and *Homo sapiens*; McHenry, 1994).

Bipedalism conferred clear advantages in this new environment, such as facilitated visual detection of food, water and predators (Shipman, 1986), as well as enabling weapon or tool use while walking (Cordain et al., 1997; Lovejoy, 1988). The biggest advantage, however, of bipedalism is considered to be the development of a more complex eccrine sweat gland system, which in turn allowed our early ancestors to walk or run over larger distances in hot climates without overheating (Cordain et al., 1997; Wheeler, 1991)[10]. Bipedalism paved the way for further changes that are seen with the rise of the genus *Homo*. *Homo habilis* had a body size similar to the *Australopithecines*, but with a markedly increased cranial capacity[11] (Cordain et al., 1997; Lieberman, 2011; Raichlen & Polk, 2013)[12]. *Homo habilis* was succeeded by *Homo erectus* who showed more similarities in body size, physique and cranial capacity to modern humans[13] (Brown, Harris, Leakey, & Walker, 1985; McHenry, 1994; Ruff, 1991). It is estimated that *Homo erectus* had better aerobic capacities than the pongids and early hominins (*Australopithecines*)(Cordain et al., 1997).

High levels of sustained activity are primarily dependent on an efficient cardiovascular system, which can be inferred from the structure of the thoracic cage and an efficient system for heat dissipation (Aiello & Wheeler, 1995). In *Homo* the upper part of the rib is able to enlarge the thorax during inhalation (Aiello & Wheeler, 1995; Cordain et al., 1997) while in *Australopithecines* and earlier species the rib cages can be narrowed during respiration in order to accommodate the muscle groups responsible for arboreal locomotion, namely the pectoral girdle (Aiello & Wheeler, 1995; Schmid, 1991). Since ventilation of the lungs depends on the movement of the diaphragm, the ability of *Homo* to enlarge the thorax suggests that they might have had a more efficient ventilation system and in turn a more efficient cardiovascular system for prolonged activities compared to pongids and *Australopithecines* (Aiello & Wheeler, 1995). Moreover, *Homo erectus* also showed a relative decrease in maximal pelvic breadth relative to stature (Ruff, 1991), which would favor better heat dissipation during intensive physical activities (such as running) even though the absolute body size had increased from earlier hominids (Cordain et al., 1997).

Because of bipedalism and efficient thermoregulation, the increased encephalization[14] of our closest ancestors progressed simultaneously with more complex behaviors and physiological changes (see for example: Bingham, 2000[15]; Dunbar, 2003), such as a larger daily range for searching for resources[16] (Leonard, 2010) and an increase in daily total energy expenditure[17] as well as an increase in size and height (Cordain et al., 1998). Larger brains inevitably require more energy[18] and through improvements in aerobic capacity of early *Homo*, larger areas could be forested to obtain high-energy diets. Raichlen and Polk (2013) have argued that increases in PA and aerobic capacity might have influenced the encephalization of modern humans directly[19]. This is in accordance with the hypothesis that early *Homo*, in order to compete with other scavengers for food, evolved a high specialization in long-distance running (Bramble & Lieberman, 2004). This adaptation would have ensured a high quality food supply, which would allow for the development of a larger brain. Regardless of what came first (larger brains or higher activity), it is clear that PA has played a large part in the evolution of modern humans.

PA is not an important aspect of modern humans' daily lives, in terms of food security, and the relationship between energy consumption and energy expenditure of modern humans has been abrogated (Cordain et al., 1997; Eaton & Eaton, 2003; Katzmarzyk, 2010). The radical advances of new technologies, the global and organized domestication of animals and the facilitation of commerce and trading have made food sources more abundant and the exertion required to obtain food supplies is lower than in any other period in human history. The estimated ratio of energy consumed over energy expended due to PA (energy efficiency ratio) is 2.25 (i.e., 1kJ of energy expenditure to consume 2.25kJ of food) for a 57-kg Stone Age human, and 3.66 for a 64-kg contemporary human (Eaton & Eaton, 2003). Essentially, modern humans spend less energy and have a higher energy input (i.e., consume more food) than their predecessors.

Additionally, humans living in modern societies are considerably less physically active than modern hunter-gatherers (Katzmarzyk, 2010). Studies investigating PF and PA of Eskimo communities (Igloolik, northern Canada), which have transitioned to a more Western lifestyle, show a reduction of PF and PA over time (from 1970 to 1990) in all age groups (Rode & Shephard, 1984; Rode & Shephard, 1994). Furthermore, a recent study comparing the energy expenditure of humans living a modern lifestyle and the Old Order Amish population, who reject modern technology, show large differences, with humans living a modern lifestyle being much more sedentary than the Amish (Bassett, Schneider, & Huntington, 2004).

In sum, even though PA has played a large part in human evolution, it has been reduced markedly in modern societies. To illustrate this point, the World Health Organization (WHO) recommends at least 150 minutes of moderate or light activity or at least 75 minutes of vigorous activity per week, but recent reports suggest that the average individual[20] does not adhere to this recommendation (Biddle & Goudas, 1996; Brawley & Rodgers, 1993; Desha et al., 2007; Sagatun et al., 2007; WHO, 2013[21]). Our genetic evolution is slower than the cultural changes that have taken place over the years and, as a result, our genes have remained adapted to the environmental circumstances of the past (Gould, 1980; p. 83). The health implications of this mismatch between human gene evolution ('hunter-gatherer genes'[22]) and human culture ('21st century lifestyle') are numerous and well documented (Cordain et al., 1997; Cordain et al., 1998; Eaton & Eaton, 2003; Katzmarzyk, Church, Craig, & Bouchard, 2009; Katzmarzyk, 2010).

Overview of Physical Activity and Health Research

From times dating as far back as Hippocrates (460 – c. 370 BC), PA has been considered a key factor for good health. Galen (129 – c. 210 AD) structured his medical theory around three concepts, the "naturals" (i.e., physiology), the "non-naturals" (i.e., health) and the "contra-naturals" (i.e., pathology). He primarily focused on the uses and abuses of the "six things non-natural"[23], which he thought were instrumental for health. These included: a) air; b) diet; c) sleep and waking; d) exercise (motion) and rest; e) excretions and retentions; and f) passions of the mind. Galen suggested that practicing the non-naturals (also known as the "six laws of health") in moderation would sustain health and prevent illness, whereas if these laws were not followed, or followed in excess, disease would be the result (Berryman, 1989; Galen, 1991).

The modern scientific field of PA research began in the early 1950s in London. Morris et al. (1953) investigated the mortality rates of London Transport Executive and Post-Office employees, and observed lower mortality rates from coronary problems in physically active employees (bus conductors and post-men) than in their sedentary colleagues (bus-drivers and telephone switchboard operators)[24]. Since then, research on the potential health benefits of PA has been flourishing. Early life PA has been shown to promote the formation of dense, well-mineralized bones (Burr, Ruff, & Thompson, 1990), as well as influence the bone structural geometry (Larsen, 1997). Moreover, an inverse association exists between PA and all-cause mortality (Paffenbarger, Hyde, Wing, & Hsieh, 1986; Powell & Blair, 1994; Salonen, Puska, Kottke, Tuomilehto, & Nissinen, 1983), cardiac events such as myocardial infarction (Balady, 2002; Myers et al., 2002), hypertension (Fagard, 2001), obesity[25] (Prentice & Jebb, 2000), and type II diabetes (Hardman & Stensel, 2003). Furthermore, PA has been associated with benefits to the immune system[26] (Pedersen & Hoffman-Goetz, 2000; Shephard & Shek, 1994) and brain function; since it increases the blood and oxygen flow in the brain (Dishman et al., 2006). Finally, PA has been positively associated with neurogenesis, gliogenesis and neuroprotection in some areas of the animal and human brain (van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999; van Praag, 2008), as well as with cognitive improvements in young children, adolescents (Chaddock, Hillman, Buck, & Cohen, 2011; Hillman, Erickson, & Kramer, 2008), and older adults (Colcombe & Kramer, 2003; Colcombe et al., 2004). The hypothesized mechanism for these benefits is the activation of neurotrophins and other growth factors, such as Brain Derived Neurotrophic Factor (BDNF).

The recognition that PA has widespread benefits on (physical) health has led to the exploration of whether the benefits of PA can also extend to well-being[27] and mental health[28]. The first epidemiological studies showed encouraging results. Stephens (1988), in a large study of over 55,000 individuals, concluded that there was a clear positive relationship between PA and well-being, positive mood and lower levels of anxiety and depression. Several later studies have also shown a positive relationship between PA and mental health (Deslandes et al., 2009; Paluska & Schwenk, 2000).

Depression imposes a burden on the health of individuals and work place productivity. The poor physical and social functioning of patients with a depressive disorder or sub-clinical depressive symptoms has been shown to be comparable to (or even worse) than the functioning of patients with major chronic medical conditions (Merikangas et al., 2007; Wells et al., 1989). Studies focusing on the impact of depression on the workplace (Kessler et al., 2006), in terms of annual salary equivalent costs, have estimated that the cost of depression-related loss of productivity in the USA is approximately $36.5 million per year. This is likely to be an underestimation of the true cost to society.

The effectiveness of depression treatments such as anti-depressant medication and behavioral therapies is still being widely debated (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010; Cuijpers, Andersson, Donker, & van Straten, 2011; Khin, Chen, Yang, Yang, & Laughren, 2011; Kirsch et al., 2008; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Therefore, there is a need for alternative effective treatments for depression, especially low cost treatments, with PA being a primary candidate. The UK National Institute for Clinical Excellence (NICE) guideline for depression recommends structured, supervised exercise three times a week (45 to 60 minutes) for 10 to 12 weeks for mild depression (National Institute for Health and Clinical Excellence, 2009). Although these Exercise Referral Schemes have been implemented, the empirical evidence of their effectiveness on depression is not robust.

For several decades now, researchers have examined the potential use of PA as an effective treatment for depression (Mead et al., 2009). Recent systematic reviews and meta-analyses of randomized controlled studies (RCTs) have shown mixed results. Krogh et al. (2010) concluded their meta-analysis by stating that there is a short-term benefit of exercise in clinically depressed patients, but very little evidence of a long-term benefit. Another meta-analysis of RCTs by Rimer et al. (2012) concluded that exercise seems to improve depressive symptoms in clinically depressed patients when compared to no treatment or a control condition. However, when only methodologically high-quality studies were included, the effect of exercise became much smaller. Mead et al. (2009) and Cooney et al. (2013) reached a similar conclusion: when only studies fulfilling three strict methodological criteria (i.e., allocation concealment, blinded outcome assessment and intention to treat trials) were analyzed, the effect sizes observed became smaller and not statistically significant. A recent large intervention study (Chalder et al., 2012) did not find any evidence that PA is beneficial for depressive symptoms[29]. However, intervention studies are only valuable in delineating whether a specific treatment is effective for depression, and do not provide information on the numerous factors that might influence the risk of developing depression and the progression of the disorder.

Since the effect of PA on depressive symptoms has been reported frequently but seems to be moderate to weak and may not even exist at all in some populations, there is a need for a better theoretical understanding of this relationship, in order to derive the best ways to maximize the potential benefit of PA in treating depression. Epidemiological studies in representative populations can be useful in elucidating multifactorial causes of the disorder and can help to provide a better theoretical framework of the relationship between PA and depressive symptoms.

Research Gaps

Most studies conducted so far have focused on adults. Studies on adolescents have been lacking; only recently has there been an increase in studies investigating the relationship between PA and depressive symptoms in adolescents. Adolescence is a period of radical physical, cognitive, and emotional change, characterized by a high incidence of depression (Hankin et al., 1998). Youth depression and adult depression are potentially different due to age-related differences in cognition, emotion, behavior, and physical development; so adult models of depression cannot be generalized automatically to children and adolescents (Abela & Hankin, 2008). Therefore, it is important to better understand the development and trajectory of depressive symptoms and their relationship with PA during adolescence.

Observational cross-sectional and prospective studies have shown mixed results in the relationship between PA and depressive symptoms in adolescents. In a meta-analysis of observational studies, Biddle and Asare (2011) showed that PA has a potentially beneficial effect on depressive symptoms, but the associations were weak and most studies suffered from serious methodological limitations. Johnson and Taliaferro (2011) reached a similar conclusion in their meta-analysis. Small to moderate protective effects of PA or sport participation on depressive symptoms were observed, but methodological limitations plagued the majority of these studies.

Besides obvious methodological problems related to this type of research, such as discrepant measures of depressive symptoms and PA and an over-reliance on cross-sectional designs (Johnson & Taliaferro, 2011), other important issues need to be addressed. One issue is the direction of the association. It is possible that PA helps to alleviate depressive symptoms (protective hypothesis), but also that depressive symptomatology hinders PA participation (inhibition hypothesis). Perhaps both, i.e., bidirectional associations, are true. Consideration of potentially moderating factors such as genetic or psychosocial variables is also vital, as these might make individuals more prone to benefit from PA, or be more adversely impacted by physical inactivity.

Aim and Objectives of this Thesis

The overall aim of this thesis is to provide a deeper understanding of the association between PA and depressive symptoms in adolescents and adults. The study in chapter II investigates the direction of the relationship between PA and depressive symptoms, while the study in chapter III investigates the hypothesis that early engagement in PA in adolescence might prevent an onset of a major depressive episode in early adulthood, and explores the role of specific characteristics of PA, i.e., the nature, frequency, intensity and duration.

The second part of the thesis focuses on possible moderators of the relationship between PA and depressive symptoms. Chapter IV examines genetic factors that might influence the extent to which adolescents benefit from PA, i.e., genes that work on important neuromodulators (such as serotonin and dopamine) and neurotrophins (BDNF). These neuromodulators and neurotrophins are thought to play an important role in the development and course of depression and also to be affected by PA. Psychosocial moderators and their influence on the relationship between PA and depressive symptoms are examined in chapter V and VI. The study in chapter V investigates whether peer-nominated sport competence and gender moderate the association of sport participation with current depressive symptoms and symptom changes over time. Chapter VI concerns the relative-age position of adolescents among their classmates, which might affect the way they are perceived on their athletic abilities by teachers, and their levels of depressive symptoms.

The final part considers individual differences in the association between PA and mood in adults. Chapter VII evaluates individual differences in the relationship between PA, as assessed with accelerometers, and repeated daily assessments of positive and negative affect in depressed and non-depressed adults. In this study, the direction of the relationship between PA and daily mood is investigated at the individual rather than at the group level.

In chapter VIII the main results of the research undertaken are summarized and discussed further, along with clinical implications and possible directions for future research.

Summary of Samples Used

The TRAILS Sample

Five out of the six empirical studies in this thesis are based on data from the Dutch TRacking Adolescents' Individual Lives Survey (TRAILS). TRAILS is a prospective population-based cohort of Northern Dutch adolescents. The general aim of TRAILS was to delineate etiologies and trajectories of (mental) health problems in the Dutch population. Data collection for the baseline measurement (T1) started in 2001 and finished in 2002. Data collection for the second (T2), third (T3) and fourth (T4) measurement waves took place at intervals of approximately 2.5 years. For this thesis, data have been used from all four measurement waves (T1 to T4). At

T1, 2230 adolescents agreed to participate. The response rates at T2, T3 and T4 were 96.4% (N = 2149; 51% girls, mean age = 13.7, SD = 0.5), 81.4% (N = 1816; 52.3% girls, mean age = 16.3, SD = 0.7) and 84.3% (N = 1881; 52.3% girls, mean age = 19.1, SD = 0.6) respectively. Detailed information on the profile, design and procedures of TRAILS have been described elsewhere (de Winter et al., 2005; Huisman et al., 2008; Nederhof et al., 2012; Ormel et al., 2012).

The MOOVD Sample

The final study of this thesis is based on data from the ongoing 'Mood and movement in daily life' (MOOVD) study, which was set up to investigate the dynamic temporal relationship between PA and mood in daily life, as well as the role of several biomarkers therein. Data collection of this study started in 2012, and the data from the first 20 individuals to participate were used (N depressed = 10; 30% males, mean age = 36.4, SD = 10.3 & N non-depressed = 10; 30% males, mean age = 36.7 and SD = 7.9). Participants were intensively monitored in their natural environment for 30 days, by means of electronic diaries, saliva sampling and continuous actigraphy. Participants were pair-matched on gender, smoking status, age, and Body Mass Index (BMI). Further details on inclusion and exclusion criteria, procedures, measures, and ambulatory sampling can be found in Chapter VII.

Notes

[1] PF will not be explored further in this thesis. The definition of PF is provided for a better understanding of the distinct terms related to PA that are sometimes used in the literature.

[2] Sometimes the energy expended during sleep, although very low, is still considered part of PA (Caspersen, Powell, & Christenson, 1985). In this thesis the energy expended during sleep was not considered as part of PA.

[3] RMR is the energy expended during quiet sitting.

[4] 1MET ≡ 1kcal/kg*h ≡ 4.184kJ/kg*h.

[5] See: oxforddictionaries.com/definition/english/sport?q=sport

[6] Slightly lower than the prevalence of depression in the USA, which is around 20% (Kessler & Wang, 2009).

[7] The *Australopithecines* are classified as hominins. The terminology has changed recently, but according to the newest terminology used there are two main distinctions: a) Hominids (hominidae), which are a taxonomic family of all modern and extinct Great Apes including humans; while b) Hominins (Homininae), is a subcategory of the Hominids, including all modern humans, extinct human species and all our immediate ancestors (*Australopithecines*, *Homo, Paranthropus* and *Ardipithecus*).

[8] *Australopithecines* walked upright (bipedalism; McHenry, 1994). The first evidence of bipedalism comes with *Australopithecus anamensis*, which is assumed to be an ancestor of the better known *Australopithecus afarensis* (Cordain, Gotshall, Eaton, & Eaton, 1998; Leakey, Feibel, McDougall, & Walker, 1995). Although the *Australopithecines* retained ape like upper limb structural features (McHenry, 1994; Stern &

Susman, 1983), some evidence from both fossilized footprints and leg bone/pelvic structure suggest that they might have walked with a relatively similar mechanical efficiency to that of contemporary humans (Lovejoy, 1988).

[9] It is still disputed whether bipedalism is as efficient, in relation to energy expenditure, as walking in quadrupeds, but this is not something that will be explored in further detail here (see for example: Halsey & White, 2012).

[10] At the same time, the evolution of attenuated body hair size ('naked' skin) also improved the evaporative cooling efficiency of the cutaneous sweat glands (Wheeler, 1992).

[11] All increases in cranial capacity are discussed in relation to body size. It should be noted, that cranial capacity does not necessarily indicate higher intelligence, since brain structure/volume is more important than actual size.

[12] The estimated brain size, relative to body size, of *Australopithecines* did not exceed 350-600cc, a size much smaller than later *Homo* species (around 700-1500cc; see figure 4, p. 6784 in McHenry, 1994) and quite similar in size to modern great apes (around 400cc in chimpanzees and gorillas; Schoenemann, 2006). There is one exception to this, namely *Homo floresiensis* (Brown et al., 2004) with an estimated brain size equal or smaller than that of chimpanzees. However, it should be noted that the study of brain sizes (paleoneurology) in extinct hominid species is hindered by the incomplete fossil record and as a result these brain sizes are approximations.

[13] At the same time of the development of a larger brain, the gut in *Homo* species started shrinking, similarly to what is observed in other carnivores, i.e., a compensation occurring at the expense of the size of the gut to accommodate a more metabolically active brain (Aiello & Wheeler, 1995; Cordain, Gotshall, & Eaton, 1997). Because the gut is not encased by bones, as is the case with the brain, the decrease in size of the gut has been estimated through differences in the anatomy (especially the abdomen and rib cages) of two early species of hominids, namely *A. afarensis* and *Homo ergaster* (Aiello & Wheeler, 1995).

[14] I.e., developing larger brains.

[15] The refined ability of humans to throw projectiles in combination with human complex social abilities (social cooperation) is also another hypothesized factor affecting our current development (for an interesting overview of this hypothesis see: Bingham, 1999 and Bingham, 2000).

[16] Which was aided by bipedalism and the ability to run large distances (at moderate pace) more efficiently than many quadrupeds (for an interesting discussion see: Bramble & Lieberman, 2004).

[17] The estimated energy expenditure of early *Homo* and modern humans was larger than that of non-human primates (Leonard & Robertson, 1997).

[18] The human brain uses around 20% of the body's energy consumption (Lassen, 1959), a percentage much higher than in other nonhuman primates (Armstrong, 1985; Armstrong, 1990) and other mammals (Armstrong, 1983).

[19] The authors base their hypothesis on the link between proximate mechanisms such as neurotrophins, PA and brain size by: a) reviewing intra and inter-specific and artificial selection studies that suggest that by improving endurance capacity these proximal mechanisms will be altered; and b) studying what is termed 'athletic species' (for more information see: Raichlen & Polk, 2013).

[20] For example, fewer than 60% of American and Norwegian adolescents adhere to these guidelines (Desha, Ziviani, Nicholson, Martin, & Darnell, 2007; Sagatun, Sogaard, Bjertness, Selmer, & Heyerdahl, 2007).

[21] who.int/dietphysicalactivity/factsheet_inactivity/en/index.html

[22] For approximately 99% of our existence as a species we have been hunters and food gatherers (Astrand, 1994).

[23] The works of Hippocrates and especially his three books on regimen, heavily influenced Galen.

[24] However these associations might be explained (better) by differences in time spent sitting rather than the activity itself (Hamilton, Hamilton, & Zderic, 2007).

[25] However, the relationship between PA and obesity is very complex (Biddle & Mutrie, 2008; p. 22).

[26] Overtraining, however, may also impair the immune system (Shephard & Shek, 1994).

[27] Since Hippocrates and Galen, anecdotal evidence or philosophical theories have been proposed on the benefits of PA on quality of life and well-being. Nonetheless, it should be noted that the terms 'well-being' and 'quality of life' are rather complex, with various different ways to measure 'well-being' and 'quality of life', whilst there are different research groups focusing on different aspects of the two (Biddle & Mutrie, 2008).

[28] It is important to note here that the distinction between physical and mental health seems to be arbitrary, since 'mental health' problems are multifactorial and probably caused by a dysfunction in both psychological and neurobiological processes (Kendler, 2012). However, this discussion is out of the scope of this thesis and the scientific nomenclature is used for clarity.

[29] This study also investigated the cost-effectiveness of a PA intervention and their findings raised doubts on whether PA is a cost-effective treatment for depression.

REFERENCES

Abela, J. R. Z., & Hankin, B. L. (2008). *Handbook of depression in children and adolescents*. New York: The Guildford Press.

Aiello, L. C., & Wheeler, P. (1995). The expensive-tissue hypothesis - the brain and the digestive-system in human and primate evolution. *Current Anthropology, 36*(2), 199-221.

Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., et al. (1993). Compendium of physical activities - classification of energy costs of human physical activities. *Medicine and Science in Sports and Exercise, 25*(1), 71-80.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders (DSM-5)* (5th ed.). Arlington, VA: American Psychiatric Association.

Armstrong, E. (1983). Relative brain size and metabolism in mammals. *Science, 220*(4603), 1302-1304.

Armstrong, E. (1985). Relative brain size in monkeys and prosimians. *American Journal of Physical Anthropology, 66*(3), 263-273.

Armstrong, E. (1990). Brains, bodies and metabolism. *Brain Behavior and Evolution, 36*(2-3), 166-176.

Astrand, P. O. (1994). Physical activity and fitness: Evolutionary perspective and trends for the future. In C. Bouchard, R. J. Shephard, & T. Stephens (Eds.), *Physical activity, fitness and health* (pp. 98-105). Champaign, IL: Human Kinetics.

Balady, G. J. (2002). Survival of the fittest - more evidence. *New England Journal of Medicine, 346*(11), 852-854.

Bassett, D. R., Schneider, P. L., & Huntington, G. E. (2004). Physical activity in an Old Order Amish community. *Medicine and Science in Sports and Exercise, 36*(1), 79-85.

Behrensmeyer, A. K., & Cooke, H. S. (1985). Paleoenvironments, stratigraphy and taphonomy in the African Pliocene and Early Pleistocene. In E. Delson (Ed.), *Ancestors: The hard evidence* (pp. 60-62). New York: Wiley-Liss.

Berryman, J. W. (1989). The tradition of the 6 things non-natural - exercise and medicine from Hippocrates through antebellum America. *Exercise and Sport Sciences Reviews/series, 17*, 515-557.

Biddle, S. J. H., & Mutrie, N. (2008). *Psychology of physical activity: Determinants, well-being and interventions* (2nd ed.). New York, USA: Routledge.

Biddle, S. J. H., & Goudas, M. (1996). Analysis of children's physical activity and its association with adult encouragement and social cognitive variables. *Journal of School Health, 66*(2), 75-78.

Biddle, S. J. H., & Asare, M. (2011). Physical activity and mental health in children and adolescents: A review of reviews. *British Journal of Sports Medicine, 45*(11), 886-895.

Bingham, P. M. (1999). Human uniqueness: A general theory. *Quarterly Review of Biology, 74*(2), 133-169.

Bingham, P. M. (2000). Human evolution and human history: A complete theory. *Evolutionary Anthropology, 9*(6), 248-257.

Bramble, D. M., & Lieberman, D. E. (2004). Endurance running and the evolution of Homo. *Nature, 432*(7015), 345-352.

Brawley, L. R., & Rodgers, W. M. (1993). Social-psychological aspects of fitness promotion. In P. Seraganian (Ed.), *Exercise psychology: The influence of physical exercise on psychological processes* (pp. 254-298). New York: Wiley.

Brown, F., Harris, J., Leakey, R., & Walker, A. (1985). Early Homo-erectus skeleton from West Lake Turkana, Kenya. *Nature, 316*(6031), 788-792.

Brown, P., Sutikna, T., Morwood, M. J., Soejono, R. P., Jatmiko, Saptomo, E. W., et al. (2004). A new small-bodied hominin from the Late Pleistocene of Flores, Indonesia. *Nature, 431*(7012), 1055-1061.

Burr, D. B., Ruff, C. B., & Thompson, D. D. (1990). Patterns of skeletal histologic change through time - comparison of an archaic Native-American population with modern populations. *Anatomical Record, 226*(3), 307-313.

Caspersen, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical-activity, exercise, and physical-fitness: Definitions and distinctions for health-related research. *Public Health Reports, 100*(2), 126-131.

Chaddock, L., Hillman, C. H., Buck, S. M., & Cohen, N. J. (2011). Aerobic fitness and executive control of relational memory in preadolescent children. *Medicine and Science in Sports and Exercise, 43*(2), 344-349.

Chalder, M., Wiles, N. J., Campbell, J., Hollinghurst, S. P., Haase, A. M., Taylor, A. H., et al. (2012). Facilitated physical activity as a treatment for depressed adults: Randomised controlled trial. *British Medical Journal (Clinical Research Ed.), 344*, e2758.

Colcombe, S. J., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14*(2), 125-130.

Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., et al. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America, 101*(9), 3316-3321.

Cooney, G. M., Dwan, K., Greig, C. A., Lawlor, D. A., Rimer, J., Waugh, F. R., et al. (2013). Exercise for depression. *Cochrane Database of Systematic Reviews,* (9), CD004366.

Cordain, L., Gotshall, R. W., Eaton, S. B., & Eaton, S. B. (1998). Physical activity, energy expenditure and fitness: An evolutionary perspective. *International Journal of Sports Medicine, 19*(5), 328-335.

Cordain, L., Gotshall, R. W., & Eaton, S. B. (1997). Evolutionary aspects of exercise. *Nutrition and Fitness: Evolutionary Aspects, Children's Health, Programs and Policies, 81*, 49-60.

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010). The effects of psychotherapy for adult depression are overestimated: A meta-analysis of study quality and effect size. *Psychological Medicine, 40*(2), 211-223.

Cuijpers, P., Andersson, G., Donker, T., & van Straten, A. (2011). Psychological treatment of depression: Results of a series of meta-analyses. *Nordic Journal of Psychiatry, 65*(6), 354-364.

de Graaf, R., ten Have, M., van Gool, C., & van Dorsselaer, S. (2012). Prevalence of mental disorders and trends from 1996 to 2009. Results from the Netherlands Mental Health Survey and Incidence Study-2. *Social Psychiatry and Psychiatric Epidemiology, 47*(2), 203-213.

de Winter, A. F., Oldehinkel, A. J., Veenstra, R., Brunnekreef, J. A., Verhulst, F. C., & Ormel, J. (2005). Evaluation of non-response bias in mental health determinants and outcomes in a large sample of pre-adolescents. *European Journal of Epidemiology, 20*(2), 173-181.

deMonocal, P. B., & Bloemendal, J. (1995). Plio-Pleistocene climatic variability in subtropical Africa and the paleoenvironment of hominid evolution: A combined data-model approach. In E. S. Vrba, G. H. Denton, T. C. Patridge, & L. H. Burckle (Eds.), *Paleoclimate and evolution with an emphasis on human origins* (pp. 262-288). New Haven: Yale University Press.

Desha, L. N., Ziviani, J. M., Nicholson, J. M., Martin, G., & Darnell, R. E. (2007). Physical activity and depressive symptoms in American adolescents. *Journal of Sport & Exercise Psychology, 29*(4), 534-543.

Deslandes, A., Moraes, H., Ferreira, C., Veiga, H., Silveira, H., Mouta, R., et al. (2009). Exercise and mental health: Many reasons to move. *Neuropsychobiology, 59*(4), 191-198.

Dishman, R. K., Berthoud, H. R., Booth, F. W., Cotman, C. W., Edgerton, V. R., Fleshner, M. R., et al. (2006). Neurobiology of exercise. *Obesity, 14*(3), 345-356.

Dunbar, R. I. M. (2003). The social brain: Mind, language, and society in evolutionary perspective. *Annual Review of Anthropology, 32*, 163-181.

Eaton, S. B., & Eaton, S. B. (2003). An evolutionary perspective on human physical activity: Implications for health. *Comparative Biochemistry and Physiology A-Molecular & Integrative Physiology, 136*(1), 153-159.

Eaton, S. B., & Konner, M. (1985). Paleolithic nutrition - a consideration of its nature and current implications. *New England Journal of Medicine, 312*(5), 283-289.

Fagard, R. H. (2001). Exercise characteristics and the blood pressure response to dynamic physical training. *Medicine and Science in Sports and Exercise, 33*(6), S484-S492.

Foley, R. (1987). *Another unique species: Patterns in human evolutionary ecology*. Harlow: Longman.

Galen, A. (1991). *On the therapeutic method* (R. J. Hankinson Trans.). Oxford: Clarendon Press.

Gould, S. J. (1980). *The panda's thumb.* W.W. Norton & Company.

Halsey, L. G., & White, C. R. (2012). Comparative energetics of mammalian locomotion: Humans are not different. *Journal of Human Evolution, 63*(5), 718-22. doi:10.1016/j.Jhevol.2012.07.008.Epub 2012 Sep 7

Hamilton, M. T., Hamilton, D. G., & Zderic, T. W. (2007). Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes, 56*(11), 2655-2667.

Hankin, B. L., Abramson, L. Y., Moffitt, T. E., Silva, P. A., McGee, R., & Angell, K. E. (1998). Development of depression from preadolescence to young adulthood: Emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology, 107*(1), 128-140.

Hardman, A. E., & Stensel, D. J. (2003). *Physical activity and health: The evidence explained.* London: Routledge.

Hasler, G., Drevets, W. C., Manji, H. K., & Charney, D. S. (2004). Discovering endophenotypes for major depression. *Neuropsychopharmacology, 29*(10), 1765-1781.

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Reviews Neuroscience, 9*(1), 58-65.

Huisman, M., Oldehinkel, A. J., de Winter, A. F., Minderaa, R. B., de Bildt, A., Huizink, A. C., et al. (2008). Cohort profile: The Dutch 'TRacking Adolescents' Individual Lives' Survey'; TRAILS. *International Journal of Epidemiology, 37*(6), 1227-1235.

Johnson, K. E., & Taliaferro, L. A. (2011). Relationships between physical activity and depressive symptoms among middle and older adolescents: A review of the research literature. *Journal for Specialists in Pediatric Nursing: JSPN, 16*(4), 235-251.

Joorman, J. (2009). Cognitive aspects of depression. In I. H. Gotlib, & C. L. Hammen (Eds.), *Handbook of depression* (2nd ed., pp. 298-321). New York: The Guildford Press.

Katzmarzyk, P. T., Church, T. S., Craig, C. L., & Bouchard, C. (2009). Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Medicine and Science in Sports and Exercise, 41*(5), 998-1005.

Katzmarzyk, P. T. (2010). Physical activity, sedentary behavior, and health: Paradigm paralysis or paradigm shift? *Diabetes, 59*(11), 2717-2725.

Kendler, K. S. (2012). The dappled nature of causes of psychiatric illness: Replacing the organic-functional/hardware-software dichotomy with empirically based pluralism. *Molecular Psychiatry, 17*(4), 377-388.

Kessler, R. C., & Wang, P. S. (2009). Epidemiology of depression. In I. H. Gotlib, & C. L. Hammen (Eds.), *Handbook of depression* (2nd ed., pp. 5-22). New York: The Guildford Press.

Kessler, R. C., Akiskal, H. S., Ames, M., Birnbaum, H., Greenberg, P., Hirschfeld, R. M. A., et al. (2006). Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. *American Journal of Psychiatry, 163*(9), 1561-1568.

Khin, N. A., Chen, Y., Yang, Y., Yang, P., & Laughren, T. P. (2011). Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. *Journal of Clinical Psychiatry, 72*(4), 464-472.

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: A meta-analysis of data submitted to the Food and Drug Administration. *Plos Medicine, 5*(2), 260-268.

Krogh, J., Nordentoft, M., Sterne, J. A., & Lawlor, D. A. (2010). The effect of exercise in clinically depressed adults: Systematic review and meta-analysis of randomized controlled trials. *The Journal of Clinical Psychiatry, 72*(4), 529-538.

Larsen, C. S. (1997). *Bioarcheology. Interpreting behavior from the human skeleton.* Cambridge: Cambridge University Press.

Lassen, N. A. (1959). Cerebral blood flow and oxygen consumption in man. *Physiological Reviews, 39*(2), 183-238.

Leakey, M. G., Feibel, C. S., McDougall, I., & Walker, A. (1995). New 4-million-year-old hominid species from Kanapoi and Allia Bay, Kenya. *Nature, 376*(6541), 565-571.

Leonard, W. R., & Robertson, M. L. (1997). Comparative primate energetics and hominid evolution. *American Journal of Physical Anthropology, 102*(2), 265-281.

Leonard, W. R. (2010). Size counts: Evolutionary perspectives on physical activity and body size from early hominids to modern humans. *Journal of Physical Activity & Health, 7,* S284-S298.

Lieberman, D. E. (2011). *The evolution of the human head*. Cambridge, MA: Harvard University Press.

Lovejoy, C. O. (1988). Evolution of human walking. *Scientific American, 259*(5), 118-125.

Lux, V., & Kendler, K. S. (2010). Deconstructing major depression: A validation study of the DSM-IV symptomatic criteria. *Psychological Medicine, 40*(10), 1679-1690.

McHenry, H. M. (1994). Tempo and mode in human-evolution. *Proceedings of the National Academy of Sciences of the United States of America, 91*(15), 6780-6786.

Mead, G. E., Morley, W., Campbell, P., Greig, C. A., McMurdo, M., & Lawlor, D. A. (2009). Exercise for depression. *Cochrane Database of Systematic Reviews (Online)*, (3), CD004366.

Merikangas, K. R., Ames, M., Cui, L., Stang, P. E., Ustun, T. B., Von Korff, M., et al. (2007). The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. *Archives of General Psychiatry, 64*(10), 1180-1188.

Morris, Jn., Heady, J. A., Raffle, P. A., Roberts, C. Q., & Parks, J. W. (1953). Coronary heart-disease and physical activity of work. *Lancet, 265*(6796), 1111-20.

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise capacity and mortality among men referred for exercise testing. *New England Journal of Medicine, 346*(11), 793-801.

National Institute for Health and Clinical Excellence (2009). *Depression: The treatment and management of depression in adults*. London: British Psychological Society and Royal College of Psychiatrists.

Nederhof, E., Jorg, F., Raven, D., Veenstra, R., Verhulst, F. C., Ormel, J., et al. (2012). Benefits of extensive recruitment effort persist during follow-ups and are consistent across age group and survey method. The TRAILS study. *BMC Medical Research Methodology, 12*(1), 93.

Ormel, J., Oldehinkel, A. J., Sijtsema, J., van Oort, F., Raven, D., Veenstra, R., et al. (2012). The TRacking Adolescents' Individual Lives Survey (TRAILS): Design, current status, and selected findings. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(10), 1020-1036.

Paffenbarger, R. S., Hyde, R. T., Wing, A. L., & Hsieh, C. C. (1986). Physical-activity, all-cause mortality, and longevity of college alumni. *New England Journal of Medicine, 314*(10), 605-613.

Paluska, S. A., & Schwenk, T. L. (2000). Physical activity and mental health: Current concepts. *Sports Medicine, 29*(3), 167-180.

Pedersen, B. K., & Hoffman-Goetz, L. (2000). Exercise and the immune system: Regulation, integration, and adaptation. *Physiological Reviews, 80*(3), 1055-1081.

Powell, K. E., & Blair, S. N. (1994). The public-health burdens of sedentary living habits - theoretical but realistic estimates. *Medicine and Science in Sports and Exercise, 26*(7), 851-856.

Prentice, A. M., & Jebb, S. A. (2000). Physical activity and weight control in adults. In C. Bouchard (Ed.), *Physical activity and obesity* (pp. 247-261). Champaign, IL: Human Kinetics.

Raichlen, D. A., & Polk, J. D. (2013). Linking brains and brawn: Exercise and the evolution of human neurobiology. *Proceedings of the Royal Society B-Biological Sciences, 280*(1750), 20122250.

Rimer, J., Dwan, K., Lawlor, D. A., Greig, C. A., McMurdo, M., Morley, W., et al. (2012). Exercise for depression. *Cochrane Database of Systematic Reviews,* (7), CD004366.

Rode, A., & Shephard, R. J. (1984). Growth, development and acculturation - a 10 year comparison of Canadian Inuit children. *Human Biology, 56*(2), 217-230.

Rode, A., & Shephard, R. J. (1994). Growth and fitness of Canadian Inuit - secular trends, 1970-1990. *American Journal of Human Biology, 6*(4), 525-541.

Ruff, C. B. (1991). Climate and body shape in hominid evolution. *Journal of Human Evolution, 21*(2), 81-105.

Sagatun, A., Sogaard, A. J., Bjertness, E., Selmer, R., & Heyerdahl, S. (2007). The association between weekly hours of physical activity and mental health: A three-year follow-up study of 15-16-year-old students in the city of Oslo, Norway. *BMC Public Health, 7,* 155.

Salonen, J. T., Puska, P., Kottke, T. E., Tuomilehto, J., & Nissinen, A. (1983). Decline in mortality from coronary heart-disease in Finland from 1969 to 1979. *British Medical Journal, 286*(6381), 1857-1860.

Schmid, P. (1991). The trunk of the Australopithecines. In Y. Coppens, & B. Senut (Eds.), *Origine(s) de la bipidie chez les hominides*. Paris: Edition du CNRS.

Schoenemann, P. T. (2006). Evolution of the size and functional areas of the human brain. *Annual Review of Anthropology, 35*, 379-406.

Shephard, R. J., & Shek, P. N. (1994). Potential impact of physical-activity and sport on the immune-system - a brief review. *British Journal of Sports Medicine, 28*(4), 247-255.

Shipman, P. (1986). Scavenging or hunting in early hominids - theoretical framework and tests. *American Anthropologist, 88*(1), 27-43.

Stephens, T. (1988). Physical activity and mental health in the United States and Canada: Evidence from four population surveys. *Preventive Medicine, 17*(1), 35-47.

Stern, J. T., & Susman, R. L. (1983). The locomotor anatomy of Australopithecus afarensis. *American Journal of Physical Anthropology, 60*(3), 279-317.

Turner, E. H., Matthews, A. M., Linardatos, E., Tell, R. A., & Rosenthal, R. (2008). Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine, 358*(3), 252-260.

van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America, 96*(23), 13427-13431.

van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience, 2*(3), 266-270.

van Praag, H. (2008). Neurogenesis and exercise: Past and future directions. *Neuromolecular Medicine, 10*(2), 128-140.

Wells, K. B., Stewart, A., Hays, R. D., Burnam, M. A., Rogers, W., Daniels, M., et al. (1989). The functioning and well-being of depressed-patients - results from the Medical Outcomes Study. *Jama-Journal of the American Medical Association, 262*(7), 914-919.

Wheeler, P. E. (1991). The influence of bipedalism on the energy and water budgets of early hominids. *Journal of Human Evolution, 21*(2), 117-136.

Wheeler, P. E. (1992). The influence of the loss of functional body hair on the water budgets of early hominids. *Journal of Human Evolution, 23*(5), 379-388.