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Physical activity and depressive symptoms

Stavrakakis, Nikolaos

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CHAPTER

VIII

Summary and General Discussion

“The great tragedy of science – the slaying
of a beautiful hypothesis by an ugly fact”

Thomas Henry Huxley, in *Collected Essays*, Vol. 8, 1870

Summary and General Discussion

Overview of the Research Objectives and Key Results

Physical activity (PA) has played a very important role in human evolution. Humans living in modern societies are relatively inactive compared to our early ancestors and modern hunter-gatherers, which clearly has led to health problems. However, the association between being physically active and developing depressive symptoms is not that clear. The overall aim of this thesis was to investigate the nature of the relationship between PA and depressive symptoms and to provide a better understanding of this relationship.

The first part of this thesis (chapters II and III) investigated the strength and direction of the relationship between PA and depressive symptoms in adolescents. The data used came from the TRacking Adolescents' Individual Lives Survey (TRAILS). More specifically, the relationship between PA and depressive symptoms was investigated prospectively (over three measurement waves spanning approximately 6 years) using Structural Equation Modeling (SEM) in chapter II. The results showed a weak bidirectional relationship between the two factors. This bidirectional relationship was observed for cognitive but not for somatic symptoms of depression. Adolescents who were more physically active were less likely to experience depressive symptoms over time, and vice versa, adolescents with more depressive symptoms were less likely to be physically active over time.

The study described in chapter III focused on the protective hypothesis of PA, by investigating its potential to prevent the onset of depression. Using a sample of adolescents, followed up for approximately 5 years, this study found no evidence that PA protected against the onset of a first major depressive episode in early adulthood in either boys or girls. Adolescents who were physically active at an early age were, regardless of the frequency, duration and intensity of the activity, equally likely to develop a first episode of depression later in life as their more sedentary counterparts.

The overall aim of the second part of this thesis was to explore possible genetic (chapter IV) and psychosocial (chapter V and VI) modifiers of the relationship between PA and depressive symptoms. The samples used were derived from TRAILS as well.

In chapter IV, the role of so-called plasticity genes in the prospective reciprocal relationship between PA and depressive symptoms was investigated. Specific alleles of these genes have been suggested to confer a susceptibility to environmental influences. This susceptibility has been hypothesized to increase with increasing numbers of plasticity alleles (Belsky & Beaver, 2011). Therefore, a cumulative plasticity index was created, in order to investigate its putative modifying effects on the relationship between PA and depressive symptoms. The individual polymorphisms were investigated as well. Overall, there was no evidence that

either the cumulative plasticity gene index or the individual polymorphisms modified the bidirectional prospective association between PA and depressive symptoms. Adolescents with genotypes assumed to reflect high plasticity did not benefit more from PA with regards to their depressive symptoms and did not exhibit more depressive symptoms after being physically inactive than individuals without these susceptibility alleles.

The study in chapter V investigated the effects of sport participation from an evolutionary perspective. We explored whether participating in competitive sports was inversely related to baseline depressive symptoms and changes in depressive symptoms over time. In addition, we examined moderating effects of peer-perceived sport competence and gender. Overall, sport participation was inversely associated with current depressive symptoms, but not with symptom changes over time. The association between sport participation and current depressive symptoms was largely explained by sport competence. Finally, there was no evidence that sport competence and gender moderated the relationship between sport participation and depressive symptoms: boys who participated in sports and were considered to be highly athletically competent did not exhibit fewer depressive symptoms than girls and less competent boys.

The study in chapter VI explored the effects of classroom positioning according to birth date in multiple domains of psychological development and other outcomes, including baseline depressive symptoms, depressive symptom changes during adolescence, and teacher-rated sport competence. In a large sample of adolescents followed for approximately 6 years, substantial relative-age effects were observed in relation to school progress: relatively younger adolescents were four times more likely to repeat a grade, while relatively older adolescents were up to 20 times more likely to skip a grade. In the subgroup that repeated a grade, the relatively young adolescents reported fewer depressive symptoms than their relatively older peers. However, the relative-age effects did not influence the evaluation of sport competence in either the normative group or the subgroup that repeated a grade.

The final part of this thesis (chapter VII)³⁰ examined temporal patterns in the association between PA and affect, using a within-subject approach (time-series analysis), with the aim to provide a better understanding of the strength and direction of the relationship between PA and affect within individuals³¹. A sample of depressed and non-depressed adults from the Mood and Movement in Daily Life (MOOVD) study was used. The results showed inter-individual differences in the strength and the sign of the relationships between PA and affect. An exception was formed by the correlations between concurrent PA and positive affect, which were positive in nearly all individuals. This suggests a consistent pattern of enhancement of positive affect during and immediately after PA, but no consistent improvement of negative affect. The longer-term (delayed) effects of PA on affect varied greatly across individuals, regardless of their depression status.

The Direction and Strength of the Relationship between PA and Depressive Symptoms

In this section, the direction of the relationship between PA and depressive symptoms will be discussed, followed by some considerations on the strength of the association, and how the findings from the studies of this thesis relate to previous research.

Direction

Chapter II describes a weak bidirectional relationship between PA and depressive symptoms in adolescents. Thus, physically active adolescents were less depressed than sedentary adolescents and adolescents with many depressive symptoms were more sedentary than those with few depressive symptoms, both cross-sectionally and over time. This finding is consistent with the results from previous studies in adolescent girls (Jerstad, Boutelle, Ness, & Stice, 2010) and older adults (Lindwall et al., 2011)³². Birkeland et al. (2009) did not find any evidence of a bidirectional relationship in a longitudinal study of adolescents between the ages of 13 and 23. Although they observed a relationship between PA and depression at age 13, changes in PA did not predict changes in depressive symptoms and vice versa. The reasons for this discrepancy are not quite clear³³. Nonetheless, the findings from chapter II support both the protective and the inhibition hypotheses previously proposed. Bidirectional relationships between PA and positive and negative affect were also found in the MOOVD study described in chapter VII, but with substantial individual differences. Some individuals exercised more when they felt better, which resulted in feeling even better, while for others this spiral was reversed or not the case at all. Individual differences in the direction of the relationship between PA and depressive symptoms are of great interest to both researchers and clinicians and should be examined in more detail, since most observational studies aggregate results across individuals and ignore differences among them systematically.

A number of mechanisms have been proposed to explain the putative benefits of PA on depressive symptoms (protective hypothesis). The predominant models include biological and psychosocial factors that are altered through PA and in turn influence the trajectory of depressive symptoms. It is important to point out that the proposed biological and psychosocial mechanisms are not in any way mutually exclusive.

The main biological mechanisms involve neuromodulators such as serotonin (5-HT; Dishman et al., 2006a), dopamine (DA; Bliss & Ailion, 1971), adrenaline and noradrenaline (NA; Dishman et al., 2006a; Helmich et al., 2010), endorphins (Boecker et al., 2008), and neurotrophins such as the Brain Derived Neurotrophic Factor (BDNF; Ploughman, 2008). Levels of these biomarkers are altered during and after exercise, which in turn triggers a cascade of changes in brain functioning that might explain the alleviation of depressive symptoms (Dishman et al., 2006a; Helmich et al., 2010; Struder & Weicker, 2001; Toups et al., 2011; van Praag,

Christie, Sejnowski, & Gage, 1999; van Praag, Kempermann, & Gage, 1999; van Praag, 2008). For example, the monoamine hypothesis of depression postulates that imbalances in 5-HT and DA³⁴ underlie features and symptoms of depression (Lapin & Oxenkrug, 1969; van Praag & Korf, 1970). Although this hypothesis has been questioned recently (Delgado, 2000; Leo & Lacasse, 2008; Luscher, Shen, & Sahir, 2011 but also see Cowen, 2008), evidence from imaging studies supports a dysfunction in 5-HT_{1A} receptors in depressed individuals (Drevets et al., 2007), and suggests that this dysfunction is not merely an artifact of antidepressant medication (Hirvonen et al., 2008). Likewise, decreased DA³⁵ activity has been linked to motoric and cognitive symptoms of depression (Nestler & Carlezon, 2006; Willner, 1995), but also to motivational problems and anhedonia in patients with major depressive disorder (MDD; Dunlop & Nemeroff, 2007). Because of interactions between the DA and 5-HT systems (Dremencov et al., 2004; Sasaki-Adams & Kelley, 2001), dysfunctions in one of these systems can initiate secondary changes in others, such as the GABA or adrenaline systems (Luscher et al., 2011; Thase, 2009).

The psychosocial mechanisms that have been proposed to explain the association between PA and depressive symptoms are based on self-determination and self-efficacy theories (Biddle & Mutrie, 2008; Deci & Ryan, 1985; Deci & Flaste, 1995; Sallis & Owen, 1999; Salmon, 2001). The rationale is that by engaging in PA, individuals become more confident in their abilities, and feel more in control. The increase in self-esteem induces an improvement in mood (Dishman et al., 2006b). There is also evidence that activities in which individuals form social networks provide a feeling of belonging and empowerment, which might result in alleviation of depressive symptoms as well (McGale, McArdle, & Gaffney, 2011). Finally, a recent review (Thompson-Coon et al., 2011) suggests that particularly outdoor activities benefit mental health. However, this area of research is relatively underdeveloped and although the initial results seem promising, future research is needed to explain the particular impact of outdoor activities on individuals' mood and depressive symptoms.

The inhibition hypothesis posits that depressed mood, at least to some degree, demotivates the individual from being physically active (Birkeland et al., 2009). Even sub-threshold depressive symptoms, i.e., symptoms that do not reach the threshold for clinical diagnosis, have been associated with psychosocial and functional impairments (Georgiades, Lewinsohn, Monroe, & Seeley, 2006; Lewinsohn, Solomon, Seeley, & Zeiss, 2000). These symptoms may trigger a negative feedback loop in which it is difficult for individuals to be energetic and motivated enough to exercise³⁶ (Goodwin, 2003). The majority of studies to date have focused on the benefits of PA on depressive symptoms, while only very few have focused on the inhibition hypothesis (Roshanaei-Moghaddam, Katon, & Russo, 2009). The findings of chapter II and VII indicate that there is a need to acknowledge the inhibition hypothesis, at least for certain individuals.

Strength of the Association

Overall, whenever a statistically significant association between PA and depressive symptoms was observed in the studies described in this thesis, the effects were weak. PA explained approximately 1 to 2% of the variance in depressive symptoms, and sport participation, regardless of the competitive element of each sport, slightly more, approximately 3 to 5%. Besides methodological limitations, which will be discussed later, there are several possible reasons why the effects were weak.

First, the weak effects might indicate that the relationship between PA and depressive symptoms is not likely to be causal. Although a plethora of hypotheses have been proposed explaining the relationship between PA and depressive symptoms, a genetic study in a large sample of monozygotic and dizygotic twins by de Moor et al. (2008) has raised doubts on the causality of the relationship. They observed cross-sectional and prospective inverse associations between leisure-time PA and anxiety and depressive symptoms, with small effect sizes. However, monozygotic twins that exercised a lot did not report fewer anxiety and depressive symptoms than their more sedentary co-twins (de Moor et al., 2008). Moreover, in the prospective analyses, changes in PA were not related to changes in anxiety and depressive symptoms, which contradicts one of the predictions made by the causal hypothesis³⁷. This indicates that the association between PA and depressive symptoms might be caused by the effects of common genes acting independently, i.e., influencing the propensity to exercise while at the same time also protecting against symptoms of depression, but without a causal link between the two.

If a long-term causal relationship exists, it may be expected that PA will exhibit clear benefits in preventing the onset of depression. This has been shown in a recent review of prospective studies in adults, adolescents and children, where PA seemed to prevent the development of depression (Mammen & Faulkner, 2013). However, the findings from chapter III do not indicate such benefits. This is contrary to the findings of a previous study (Jacka et al., 2011), based on a large Australian study in over 2000 adults (median age 56 years), in which PA during childhood and depression in later life were retrospectively measured. In this study, low levels of self-reported childhood PA increased the odds of reporting depression in adulthood by 35%. Even though these findings might be affected by retrospective bias, it is still possible that PA prevents depression onset in middle to late adulthood where the average onset of MDD is estimated to be between the ages of 20 and 30³⁸ (Kessler & Wang, 2009).

A second reason for the weak associations between PA and depressive symptoms could be that the relationship between PA and depressive symptoms is modified by other factors. For example, puberty, school transitions and other important life changes, biological factors, social factors, sleep and diet, and personality traits may all affect both one's mood and

engagement in PA, and perhaps also moderate the relationship between the two. Chapters IV, V and VI investigated some of these factors in more detail and their impact is discussed in the next section.

Another possible reason for the weak associations is that PA may have a differential relationship with different clusters of depressive symptoms. Chapter II showed that PA was inversely associated with the cognitive symptom but not with the somatic symptom subscale of depression³⁹. This difference might have been due to the low reliability of the somatic symptom subscale of depressive symptoms⁴⁰. Possibly, individual somatic symptoms are differentially related to PA, for instance, PA could be inversely related to sleep problems and positively related to energy levels. Currently, there is a lack of studies examining this possibility.

Finally, the weak effects might reflect that PA is beneficial in reducing depressive symptoms for some individuals but not for all⁴¹. In large-scale epidemiological studies like TRAILS, information is aggregated from groups of individuals (between-subject design) and group averages of the association between PA and depressive symptoms are presented⁴². Even large effects at the group level, however, may not apply to fluctuations within individuals, since a between-subject correlation is not the same as a within-subject correlation (Hamaker, Dolan, & Molenaar, 2005; Molenaar & Campbell, 2009; Rosmalen, Wenting, Roest, de Jonge, & Bos, 2012). This between-subject variability needs to be taken into account when studying the relationship between PA and depressive symptoms, in order to avoid unjustified inferences of group-level findings with regard to temporal patterns within individuals (de Jonge & Bos, 2013; Hamaker, 2012; Molenaar & Campbell, 2009). To learn how PA and affect influence each other over time within persons, studies using time-series analysis⁴³ with a large number of repeated assessments per person offer a great research tool. The results of the study in chapter VII suggest that PA had a consistent positive short-term influence on positive affect for the majority of participants, but not on negative affect. This finding is in line with the majority of ecological momentary assessment (EMA) studies, which have generally shown that the relationship between PA and positive affect is more consistent than the relationship between PA and negative affect (Kanning et al., 2013). However, even though the majority of individuals showed a consistent positive relationship between PA and positive affect, only for a few individuals (5 out of 19) was this relationship significant and of at least moderate strength. This indicates that, even though for some individuals the relationship was moderate, a group aggregation approach would most likely dilute the effects and be weak over all participants. This was even more pronounced in the relationship between PA and negative affect, where the associations were very heterogeneous among individuals, that is, some participants showed a negative association, a few others a positive one⁴⁴. Therefore, the results from the study in chapter VII indicate that the weak effects found in prior chapters are probably due to individual heterogeneity in the relationship between PA and affect. Future

studies should use a combination of between- and within-subject approaches, in order to identify commonalities between individuals and elucidate why some individuals benefit or are harmed by PA in relation to their mood.

Genetic and Psychosocial Modifiers

The second part of this thesis (chapters IV, V and VI) explored possible genetic and social modifiers of the PA-depressive symptom relationship. Both will be discussed in the following part.

Genetic Modifiers

Belsky et al. (2009) identified a number of genes that are thought to be involved to susceptibility to environmental influences, and have been labeled plasticity genes. The plasticity genes hypothesis extends the classic diathesis-stress model⁴⁵, by stating that individuals with a specific genotype will not only be at increased risk when exposed to negative life events and experiences, but also benefit more from positive ones, such as social support⁴⁶ (Belsky & Pluess, 2009; Belsky et al., 2009; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). These putative plasticity genes, which were investigated in chapter IV, influence mainly the serotonergic and dopaminergic system, and have been shown to act in a ‘For better and for worse’ manner consistently in the literature (Belsky & Pluess, 2009; Belsky et al., 2009). In the study described in chapter IV, there was no evidence to suggest that either the cumulative plasticity index or the individual polymorphisms modified the bidirectional relationship between PA and depressive symptoms prospectively.

This is contrary to findings from three recent studies. Two studies on the serotonin transporter polymorphism (*5-HTTLPR*; Rethorst, Landers, Nagoshi, & Ross, 2010 and Rethorst, Landers, Nagoshi, & Ross, 2011) concluded that carriers of the short allele of *5-HTTLPR* had a larger reduction in depressive symptoms following exercise than carriers of the long allele. Another study, which concerned the *BDNF* val/met polymorphism, showed that carriers of the met allele that exercised more exhibited fewer depressive symptoms than carriers of the val allele (Mata, Thompson, & Gotlib, 2010). Both were cross-sectional studies conducted in adults with relatively small sample sizes, and investigated the role of these genes in the unidirectional effect of PA on depressive symptoms. In contrast, the study in chapter IV was prospective and investigated the moderating effects of these genes on the bidirectional relationships between PA and depressive symptoms in a large population sample of adolescents. Therefore, differences in the design and the population sample might account for the discrepant findings.

Mixed findings concerning the *5-HTTLPR* gene and especially the gene-environment interaction of the short allele on depression are ubiquitous in the literature (Caspi et al., 2003;

Karg, Burmeister, Shedden, & Sen, 2011; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009). Therefore, the influence of the short-allele of the *5-HTTLPR* as a moderator of the relationship between PA and depressive symptoms remains inconclusive. The discrepant findings concerning the *BDNF* gene are more surprising, considering the large body of research showing that BDNF levels are altered by PA (Toups et al., 2011; van Praag et al., 1999; van Praag, 2008) and changes in BDNF levels are implicated with depression⁴⁷ (for a review see Hashimoto, 2010). It is possible that this discrepant finding is due to methodological limitations of our study: since the number of participants homozygous to the met allele was small, we merged this group with the individuals carrying the met/val alleles, which may have introduced bias in the results.

The *BDNF* and other plasticity genes have numerous polymorphisms, of which only a small selection were investigated in our study. Investigation of additional polymorphisms may help to identify genetically based subgroups of individuals that will benefit from PA with regard to their depressive symptoms⁴⁸. However, considering the difficulties and inconsistencies with candidate genes replications in MDD (Flint & Kendler, 2014), among other disorders, this is speculative. Depressive disorders are multifactorial and due to the inability to identify clear candidate genes for these ailments, we cannot exclude the possibility that multiple genes and their interactions influence their onset and trajectory. This polygenic effect of multiple loci of genes interacting has been recently investigated in several psychopathologies, including MDD, and yielded some promising results (Peyrot et al., 2014; Smoller et al., 2013). Future research is needed to elucidate the complex interactions between genes and their influence on behavior, but there are reasons for optimism in this line of research.

Psychosocial Modifiers

Two possible psychosocial modifiers of the relationship between PA and depressive symptoms have been explored, namely sport competence as perceived by peer evaluations and classroom positioning according to the month of birth.

PA, Sport Participation and Sport Competence

The competitive element of sport participation has been argued to have an evolutionary origin (Lombardo, 2012) for several reasons. First, sports resemble primitive hunting and warfare of our ancestors. Second, sports are universal and can be found in almost every human group throughout history. Finally, athletic competitions play a very influential role in society. Lombardo argued that the competitive element of sports influences hierarchy formations in males. This hierarchy formation will in turn affect the chances of males being selected by females as sexual partners (Lombardo, 2012).

In turn, this hierarchy formation has been linked to depression⁴⁹. Price et al. (1994) suggested in their Social Competition Hypothesis that depression might be an adaptive strategy, similar to hibernation in some animals⁵⁰. Hence, individuals who are likely to lose in ritual agonistic competitions may develop depression in order to be protected from further damage and loss of their position within a social group⁵¹. In other words, the Social Competition Hypothesis predicts that lower status individuals are more likely to suffer from depression.

The study in chapter V investigated whether the Social Competition Hypothesis extends to sport participation and depressive symptoms. Overall, there was a positive association between adolescents who participate in competitive sports and social status, supporting the hypothesis that sport participation acts as a hierarchy formation in adolescents⁵². This is consistent with other studies showing that sport participation, especially in boys, is important for adolescent hierarchy formation (Gill, 1992). Moreover, sport competence was also related to concurrent depressive symptoms, as was suggested by Price et al. (1994), i.e., relatively incompetent individuals exhibited more depressive symptoms⁵³. Sport competence explained the observed relationship between sport participation and depressive symptoms, which indicates that sport competence may have a larger influence on depressive symptoms than participation in sports. There was no evidence that sport participation and sport competence were related to changes in depressive symptoms. Furthermore, boys who were considered to be highly sport competent did not benefit more from sport participation than girls or less competent boys.

PA has had an important role in the evolution of humans, thus any beneficial effects of PA on depressive symptoms could be put into a larger evolutionary theoretical framework. Our study supported some predictions based on these evolutionary perspectives, but not the whole postulated relationship between PA, sport participation and depressive symptoms. It is important to investigate the relationship between PA or sport participation and depressive symptoms from an evolutionary perspective, because through this larger framework important insights can be achieved. Evolutionary perspectives offer the possibility for new hypotheses to be tested, which can lead to a better understanding of the relationship between PA and mental health.

Classroom Positioning and Relative-Age Effects

Children are allocated into classrooms according to their date of birth⁵⁴. This might result in classrooms encompassing children of up to a year older being in the same grade with relatively younger children. Previous research has shown relative unfavorable outcomes in certain domains for the relatively young compared to the relatively old children (see for example: Bedard & Dhuey, 2006 and Morrow et al., 2012). These favorable or unfavorable outcomes might be a result of the evaluation of adults or their peers. Relative older

adolescents will be slightly taller, stronger and physically more mature, which would result in a higher likelihood to be selected by coaches and excel in sports (Gladwell, 2008)⁵⁵. If being perceived or being actually competent in sports influences social status (as was shown, to some extent, in chapter V) then the relative older adolescents might report fewer depressive symptoms through this attainment of higher status (as shown in chapter V as well). Thus, the relative-age effects might moderate the relationship between PA and depressive symptoms. Although not directly explored here, the possibility that relative-age effects influence hierarchy formations and so result in better opportunities for the relative older individuals appears to be a promising line for future research. The findings in chapter VI indicated that there are no relative-age effects (favorable or unfavorable) in adolescents with a normative school progress. However, within adolescents who repeated a grade, the relative young ones reported fewer depressive symptoms than their relatively older peers. These relative-age effects did not translate into differences in the evaluation of sport competence by teachers, in either group. The possibility that these relative-age effects influence peer perceptions of sport competence was not considered. Chapter V showed a difference in the perceptions of sport competence between teachers and peers. Hence, it would be interesting to explore how peer perceptions might be affected by relative-age differences.

In sum, most of the moderation analyses performed in the studies in this thesis have not yielded clear factors that might help identify individuals that can benefit or be harmed by PA, regarding depressive symptomatology. The study in chapter VII, however, showed individual differences in the relationship between PA and affect, which still suggests that there might be common factors between individuals that influence whether PA can be beneficial for mental health. Future research using a combination of within and between subject designs might prove imperative in identifying these common factors. The elucidation of the reasons why some individuals benefit from PA while others do not, might prove helpful in the development of individual-targeted PA interventions that will be effective in treating depression.

Strengths & Limitations

The longitudinal design and the large sample sizes used in most chapters is an important strength of this thesis. In most cases, sample sizes of more than 1000 adolescents were used, which provided adequate power to detect relatively small effect sizes. Additionally, we used two or more measurement waves, covering a relatively long period of time. This facilitates the exclusion of time-invariant unobserved individual differences and informs of the temporal order of events, thus making the exploration of the direction of the effects under investigation possible.

There are also limitations that need to be acknowledged. In most studies in this thesis, self-report measures of PA and depressive symptoms were used, with different degrees of

specificity. Self-reports typically depend on the memory of participants, who estimate their depressive symptoms or PA based on an average week. The affective scale of the Youth Self-Report, which assesses depressive symptoms corresponding to DSM-IV criteria (Achenbach & Rescorla, 2001), is an empirically based and well-validated questionnaire with an acceptable test-retest reliability (Achenbach, Dumenci, & Rescorla, 2003). However, the use of self-reports to estimate PA has been criticized by researchers (see for example: Johnson & Taliaferro, 2011), since these might be prone to over or under-estimation of the levels of PA engagement. Although acceptable test-retest reliability was shown in independent samples (Booth, Okely, Chey, & Bauman, 2001; Haskell, 2012)⁵⁶, recent reviews comparing self-reports to more direct measures of PA, such as accelerometers, revealed only a moderate to weak correlation between the two (Adamo, Prince, Tricco, Connor-Gorber, & Tremblay, 2009; Prince et al., 2008). For example, Adamo et al. (2009) observed that self-reports underestimated light or moderate PA, while vigorous PA was consistently over-estimated, when compared to more direct measures in children and adolescents. Prince et al. (2008) found that studies using self-reports generally overestimated the levels of PA participation when compared to direct measures, especially for women. Another limitation is that, throughout this thesis, the relationship between PA and depression was modeled using linear regression techniques. It is possible that PA is beneficial up to a certain point (curvilinear relationship), while exceeding this threshold results in adverse mental health consequences, as studies on the negative effects of overtraining on mood have shown (Bresciani et al., 2011; Armstrong & VanHeest, 2002). In most chapters of this thesis, the effects of duration and intensity of PA were not considered. It is possible that only individuals who engage at a specific frequency, duration and intensity of PA experience fewer depressive symptoms (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Goldfield et al., 2011; Sanders, Field, Diego, & Kaplan, 2000). A study in Chinese adolescents (Tao et al., 2007), for example, showed that only low to moderate PA intensity but not high intensity was related to depressive symptoms. Therefore, it is possible that the different intensities of PA might have a differential association with depression. However, in the study in chapter III we examined the dose-response effect of PA and found no evidence that different frequencies, durations and intensities of activities protected against an onset of depression. To conclude, it is still possible that the different durations and intensities of activities differentially relate to depressive symptoms, but based on the results in this thesis, this seems unlikely.

Clinical Relevance

Throughout this thesis, the effect sizes observed were small. Still, weak effects observed in population studies (epidemiology) do not necessarily imply that the use of PA or exercise in a clinical trial cannot alleviate such symptoms. Findings from population studies cannot

be used to justify exercise as a treatment without relying on randomized controlled trials (RCTs), regardless of the strength of the relationship observed in these studies. Even small effect sizes found in population studies can translate to substantial clinical benefits in certain individuals. To illustrate this point, Rosenthal showed that prescribing aspirin resulted in a substantial decrease in heart attacks (85 out of approximately 11000 patients), despite the estimated effect being weak ($r = -.03$; Rosenthal, 1990)⁵⁷.

Concerning the relationship between PA and depression, initially promising results (in both observational and intervention studies) have been prematurely echoed and exaggerated⁵⁸, mainly because of the elegant and intuitively appealing hypothesis that PA might be used as a treatment for depression. Some support for this hypothesis was observed in the study in chapter VII⁵⁹. The results suggested that, although higher levels of PA resulted in lower negative affect in a few subjects⁶⁰, there were also individuals in whom high levels of negative affect were associated with more activity. This may indicate that for some individuals PA may be an efficient strategy to alleviate negative mood. However, a recent high quality RCT (Chalder et al., 2012) and meta-analyses of RCTs (Cooney et al., 2013; Mead et al., 2009) have not found sufficient support for this hypothesis at the group level⁶¹.

Finally, the results in chapter VII indicate that PA has a direct effect on elevating positive mood for the majority of individuals, regardless of whether they are depressed or not, but the delayed effect of PA on positive mood seems to be much less consistent. The reasons for a short-term effect of PA on positive affect, and for why this does not carry over to longer time periods, are currently not understood. Cogent and elegant hypotheses implicating biological factors such as the endorphin system⁶² (Dishman & O'Connor, 2009; Thoren, Floras, Hoffmann, & Seals, 1990) have been proposed, but future research is needed to investigate these mechanisms in further detail. By identifying the reasons why these benefits do not carry over the longer term, clinicians might be able to manipulate factors and identify specific individuals that might be helped by PA in terms of their depressive symptoms. Until a better understanding is achieved, however, any conclusions about this relationship should be tentative and conservative until further studies demonstrate substantial clinical benefits that are specific to PA.

Concluding Remarks

The relationship between PA and depressive symptoms has been investigated extensively over the last few years. Initial studies bore the promise that PA might reduce depressive symptoms, which would make it a very elegant and potentially cost-effective treatment for depression. Major organizations such as the WHO have implemented exercise referral schemes for the treatment of depression. However, some authors have questioned the cau-

sality of the relationship between PA and depressive symptoms (Birkeland et al., 2009; de Geus & de Moor, 2008; de Moor et al., 2008), while others have argued that the protective effects of exercise might have been overestimated (Daley & Jolly, 2012).

This thesis illustrates that the relationship between PA and depressive symptoms is bi-directional, not robust and more complex than what was previously envisioned. This suggests that PA might not be directly related to mental health but instead represents a small fraction in a large dynamic network of factors interacting with each other. Additionally, this thesis demonstrated large inter-individual differences in the relationship between PA, affect and depressive symptoms, where some individuals benefited from PA, while others did not. It was also evident that for some individuals depressed mood hindered them from being physically active, while for others this negative mood motivated them to ‘walk it off’.

Future research should focus on delineating other factors that influence the relationship between PA and depressive symptoms, in order to accurately identify individuals that might benefit from PA. This accurate identification of individuals will hopefully help to devise personal exercise interventions for treating depression.

Notes

- ³⁰ This study has many differences from all other studies included in this thesis and therefore has been included in a separate section. However, because this study explored the strength and the direction of the relationship between PA and affect in individuals, the findings will be discussed in parts of the discussion that are most relevant.
- ³¹ Affect is thought to be the most elementary form of a conscious feeling and is defined as “a neurophysiological state that is consciously accessible as a simple, non-reflective feeling that is an integral blend of hedonic (pleasure-displeasure) and arousal (sleepy-activated) values” (see: Russell, 2003, table 1). A prolonged core affect leads to what is termed mood. Affect is divided into positive affect and negative affect. Long lasting changes on affect and especially increases in negative affect can lead to a depressed mood (Clark & Watson, 1991), and consequently a prolonged depressed mood can lead to further exacerbation of depressive symptoms and subsequently to the development of depression. This study explored the influence of PA on positive and negative affect in depressed and non-depressed individuals because of the close connection between affect and depressed mood.
- ³² Lindwall et al. (2011) established that the direction of the relationship was stronger from PA to depressive symptoms than the other way around, but the model fit suggested that the relationship was bidirectional.
- ³³ Numerous reasons could be behind this discrepancy, but most of these are speculative. For instance, it could be that Birkeland et al.’s results reflected a false negative. Perhaps the protective and inhibition hypotheses are true only in adulthood and not in adolescence. It is also possible that the results of Birkeland et al. were due to a narrow definition of PA. Birkeland et al. focused on leisure-time PA, which, according to some authors, should be considered as exercise and not PA (Caspersen, Powell, & Christensen, 1985). Finally, the relationship between PA and depressive symptoms might not be a causal one (this point will be elaborated further in later parts of this thesis).

- ³⁴ NA has also been implicated in depression (Thase, 2009).
- ³⁵ It should be noted that most antidepressants do not seem to directly impact DA levels. However, MAOIs, bupropion and sertraline have been shown to have some effect on dopaminergic neuromodulation in animal models of depression (Thase, 2009; Willner, 1995; Willner, 1997). Moreover, in animals these antidepressants countermand dysfunctions in DA systems, especially in conditions of chronic stress (Cuadra, Zurita, Gioino, & Molina, 2001; Nestler & Carlezon, 2006). Therefore, DA and its possible effect on depression is of great interest for future research.
- ³⁶ Similarly, a positive mood may result in higher energy levels and motivation, which can influence engagement in PA.
- ³⁷ The causal hypothesis on the relationship between PA and depressive symptoms, with the protective and inhibition hypotheses as two specifications, predicts that increases in frequency and intensity of PA over time would reduce depressive symptoms over time, and conversely, that decreases in PA levels over time would increase depressive symptoms over time, through a causal chain.
- ³⁸ With a later peak between the ages of 30 and 40 (see: <http://www.health.am/psy/major-depressive-disorder/>).
- ³⁹ Cognitive symptoms subscale includes: lack of interest; feelings of worthlessness; loss of pleasure; crying; self-harm; suicidal ideation; and feelings of guilt and sadness. The somatic symptoms subscale includes: lack of appetite; overtiredness; trouble with sleeping and lack of energy.
- ⁴⁰ This finding is counter-intuitive, because it would be expected that PA, if anything, improves sleep quality, increases appetite and (unless overtraining) increases energy levels (Biddle & Mutrie, 2008). Furthermore, a recent study has shown that PA reduced somatic symptoms of depression in patients with chronic heart failure (Redwine et al., 2012).
- ⁴¹ Note here that the modifying analyses in this thesis explored this idea further, without conclusive findings. The study in chapter VII, however, showed individual differences in the relationship between PA and affect more clearly and these findings will be discussed in this section.
- ⁴² Between-subject designs are also called *nomothetic* approaches, while within-subject designs are also called *idiographic* approaches. Because the terms 'nomothetic' and 'idiographic' are not used in the originally intended way (Lamiell, 1998), the terms between-subject and within-subject designs are used instead, in order to avoid any further confusion.
- ⁴³ Which is a within-subject approach measuring the same individual over multiple measurement points. Although this approach cannot compare effects between individuals, it can elucidate the pattern of the relationship in individuals over time.
- ⁴⁴ It should be noted here, that these results could be interpreted differently. It could be argued that the relationship between PA and negative affect was rather homogeneous, since the majority of participants did not show an effect of PA on negative affect or vice versa. However, the fact that some individuals showed positive while others showed negative associations between PA and negative affect, even though a minority, should make it clear that there is some heterogeneity in the association between these two factors.
- ⁴⁵ Individuals with specific genotypes (diathesis) might be vulnerable to developing mental health problems after important negative life events (stressors) have occurred.
- ⁴⁶ This is referred to as 'For better and for worse'.
- ⁴⁷ BDNF is targeted by a variety of antidepressants (Hashimoto, 2010). In MDD and Bipolar Disorder (BPD) studies, antidepressant medication increased the expression of *BDNF* mRNA in limbic structures in response to chronic treatment but not acute treatment (see for example: Hashimoto, 2010). Finally, the time that it takes to increase BDNF expression coincides with the time typically required for antidepressants to work in depressed patients (Hashimoto, 2010).

- ⁴⁸ Or conversely increase vulnerability to depression that in turn can affect PA engagement levels.
- ⁴⁹ This hypothesis is consistent with gender differences observed in depression and has been dealt with in previous publications from the authors (Price, 1988). Briefly, they suggest that females still compete for ranking, but female competition is more inconspicuous and less common than male competition.
- ⁵⁰ Notably, not all evolutionary perspectives converge on the idea that depression might be adaptive (Allen & Badcock, 2006; Nettle, 2004). Some theories propose that personality traits, such as neuroticism, might be adaptive and therefore survived evolution. Individuals, who are on the far side of this affective reactivity distribution will suffer detrimental effects, i.e., develop depression (Nettle, 2004).
- ⁵¹ Throughout the early human evolutionary history, this loss would have likely resulted in physical harm, lower chances of reproduction or death.
- ⁵² And as such, supported the prediction made by the evolutionary perspective of sport participation (Lombardo, 2012), i.e., more athletically competent individuals will attain higher status.
- ⁵³ Therefore also supporting one of the predictions of the Social Competition Hypothesis (Price et al., 1994) that lower status individuals will suffer more from depressive symptoms than higher status individuals.
- ⁵⁴ There is considerable variation to this rule in different cultures (Bedard & Dhuey, 2006).
- ⁵⁵ Especially since in childhood and adolescence even small differences in age (a year or less) result in large differences in physique and abilities.
- ⁵⁶ Even a single item is considered to provide an accurate representation of an individual's engagement in PA (Milton, Clemes, & Bull, 2012).
- ⁵⁷ This might seem as a rather small proportion of people being protected, but this clinical trial was terminated prematurely, because the evidence that aspirin protected from heart-attacks was so overwhelming that it was deemed unethical to continue giving placebo medication to the control group (see Rosenthal, 1990).
- ⁵⁸ There are intervention studies that show a benefit of PA on depressive symptoms (see for example: Blumenthal et al., 1999 and Brown, Pearson, Braithwaite, Brown, & Biddle, 2013) but have been criticized for low quality methodological designs including: small samples, short follow-ups, poor randomization, no adequate control group and reliance on non-clinical volunteers (Daley & Jolly, 2012). Adding to these problems the possibility of publication bias, it is imperative to design intervention studies of high methodological quality in order to conclusively demonstrate that PA can be used as a treatment for depression.
- ⁵⁹ Although not an intervention study.
- ⁶⁰ And therefore supporting (to an extent) the bidirectional relationship observed in prospective (observational) studies.
- ⁶¹ Also see a review on EMA studies by Kanning et al. (2013).
- ⁶² Briefly, this theory suggests that PA increases endorphin levels, resulting in what colloquially is termed 'Runner's high'. These changes have been shown to last only for a very brief period of time.

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Summary in English

Depression is a global public health problem, mainly because of the relatively high lifetime prevalence and the substantial disability of individuals afflicted with this disorder. In the general population, an estimated one out of 20 people will suffer from major depression at any given point in time. The causes of the disorder include a complex interaction of psychological, biological and behavioral factors, which makes depression difficult to treat. The effectiveness of current interventions to treat depression, such as cognitive behavioral therapy and antidepressant medication, are intensely debated. In the last few decades, research has focused on the potential benefits of physical activity in treating depression. Early studies suggested that physical activity might be effective in alleviating depressive symptoms, thus providing new grounds for optimism and potentially offering a valuable intervention for the treatment of depression. However, the evidential base for this optimism is not very strong, especially concerning depressive symptoms in adolescents.

The aim of this dissertation was to explore in depth the relationship between physical activity and depressive symptoms in adolescents and adults. A better understanding of the direction and strength of this relationship and identification of possible moderators may contribute to an effective prevention and treatment of depression. The research described in this thesis was part of the studies Tracking Adolescents' Individual Lives Survey (TRAILS) and Mood and Movement in Daily Life (MOOVD). TRAILS has followed a large cohort of Dutch adolescents from early adolescence up until adulthood. MOOVD examines the temporal relationship between physical activity and mood in daily life in depressed and non-depressed adults.

In *chapter II*, the direction of the relationship between physical activity and depressive symptoms was explored and discussed. Previous research has primarily focused on the effects of physical activity on depressive symptoms, and largely ignored the potential effects of depressive symptoms on physical activity. We observed a bidirectional prospective relationship. Adolescents who were active exhibited fewer depressive symptoms over time than more sedentary adolescents, and the opposite was also true, that is, adolescents with many depressive symptoms became more sedentary over time than adolescents with fewer depressive symptoms. Cognitive symptoms of depression such as loss of interest and depressed mood were more likely to be associated with physical activity than somatic symptoms such as loss of appetite, sleep and energy.

The study described in *chapter III* investigated the protective hypothesis of physical activity, which states that early engagement in physical activity might prevent the onset of depression. This was explored regarding the period from adolescence to early adulthood, which spanned approximately 6 years. Effects of specific characteristics of physical activity, i.e., its nature, duration, frequency and intensity, were examined in the analysis. Physical

activity did not protect against a first episode of depression in this study, so the hypothesis that early physical activity might prevent the onset of depression was not supported empirically.

Chapter IV concerns the potential role of so-called plasticity genes on the (bidirectional) relationship between physical activity and depressive symptoms. The term plasticity genes refers to polymorphisms that have been reported to influence the actions of some neuro-modulating and neurotrophin systems. These systems, among which are the serotonergic and dopaminergic systems, can be altered by physical activity and depression. Overall, adolescents with these polymorphisms assumed to reflect high plasticity did not differ from other adolescents with regard to any of the associations between physical activity and depressive symptoms. In other words, we found no evidence that the proposed genes directly influence the relationship between physical activity and depressive symptoms.

The study in *chapter V* explored whether adolescents participating in competitive sports reported fewer concurrent depressive symptoms and developed fewer depressive symptoms over time. In addition, we examined the influence of peer-perceived sport competence and gender on the relationship between competitive sport participation and depressive symptoms. Overall, both boys and girls who took part in competitive sports reported fewer concurrent depressive symptoms, but did not differ from others with regard to symptom changes over time. The association between sport participation and concurrent depressive symptoms was largely explained by peer-perceived sport competence. This indicates that athletically competent adolescents are less likely to exhibit depressive symptoms, regardless of their competitive sport participation.

Chapter VI concerns the effects of classroom positioning according to birth dates on multiple outcomes, including depressive symptoms, depressive symptom changes during adolescence, and teacher-rated sport competence. Substantial relative-age effects were observed in relation to school progress: relatively young adolescents were four times more likely to repeat a grade than the relatively old adolescents, while relatively old adolescents were up to 20 times more likely to skip a grade. In the subgroup of adolescents who had repeated a grade, the younger ones exhibited fewer depressive symptoms than relatively older peers who had repeated a grade. Finally, the relative-age effects did not influence the evaluation of sport competence in either the normative group or the subgroup that repeated a grade.

The final empirical chapter of the thesis (*chapter VII*) examined the relationship between physical activity and affect in depressed and non-depressed adults, using a within-subject approach. During a month, physical activity and affect (positive and negative) were measured three times a day by means of accelerometers and diaries. The results showed individual differences in both the direction and the strength of the relationships. Cross-sectional

correlations between physical activity and positive affect were positive in nearly all individuals, though not always significant, which suggests that positive affect was enhanced during and immediately after physical activity. No consistent improvement was observed in negative affect. The long-term effects of physical activity on positive and negative affect varied greatly across individuals, regardless of their depression status. While for a few individuals physical activity improved (positive) affect in the long term, for the majority of individuals the relationship did not exist or was even reversed.

In conclusion, this thesis confirms the existence of a relationship between physical activity and depressive symptoms, but it is rather weak, and shows substantial individual differences. Some individuals tend to feel better after having been physically active, while others feel worse or show no relationship between mood and activity. The reasons behind these differences are still unknown, and we do not know yet which individuals might benefit from an active lifestyle. This knowledge is needed to design effective personalized interventions for the treatment of depression. Up to this point, however, the evidence that physical activity can help treat depressive symptoms is relatively weak, and additional research is required before physical activity can be implemented as an effective strategy for the treatment of depression.

Summary in Dutch

Depressie is een wereldwijd gezondheidsprobleem. Dit komt voornamelijk doordat relatief veel mensen een depressie doormaken in hun leven, maar ook omdat depressie gepaard kan gaan met fors functieverlies. Naar schatting 1 op de 20 mensen krijgt gedurende de levensloop een depressieve stoornis. De oorzaken van depressieve stoornissen omvatten een complexe interactie van psychologische, biologische, en gedragsmatige factoren, hetgeen depressie lastig te behandelen maakt. De effectiviteit van de beschikbare interventies voor depressie, zoals cognitieve gedragstherapie en antidepressieve medicatie, zijn onderwerp van hevig debat. Wetenschappers hebben zich de afgelopen decennia gericht op de potentiële voordelen van lichamelijke beweging als alternatieve behandeling van depressie. Tot dusver hebben enkele studies laten zien dat lichamelijke beweging effectief kan zijn in het verminderen van depressieve symptomen en dus een waardevolle aanvulling kan zijn. Er is echter nog weinig bewijs voor dit optimisme, in het bijzonder met betrekking tot depressieve symptomen in de adolescentie.

Het doel van dit proefschrift is om de associatie tussen lichamelijke activiteit en depressieve symptomen uit te diepen. Een beter begrip van de richting en sterkte van de associatie tussen lichamelijke (in)activiteit en depressieve symptomen en identificatie van mogelijke moderatoren kan bijdragen aan het voorkomen en behandelen van depressie. Het proefschrift beschrijft onderzoek dat is uitgevoerd in de studies TRAILS ('Tracking Adolescents' Individual Lives Survey') en MOOVD (Mood and Movement in Daily Life). TRAILS volgt een groot cohort van Nederlandse adolescenten van de vroege adolescentie tot in de volwassenheid. MOOVD onderzoekt de temporele relatie tussen lichamelijke activiteit en stemming in het dagelijks leven in depressieve en niet-depressieve volwassenen.

In *hoofdstuk II* wordt de richting van de verbanden tussen lichamelijke activiteit en depressieve symptomen verkend en bediscussieerd. Eerder onderzoek was voornamelijk gericht op de effecten van lichamelijke activiteit op depressieve symptomen, terwijl de potentiële effecten van depressieve symptomen op lichamelijke activiteit grotendeels werden genegeerd. In onze studie werd een wederkerige relatie geobserveerd. Adolescenten die actief waren ervoeren minder depressieve symptomen op het volgende meetmoment dan adolescenten die minder bewogen, maar het tegenovergestelde was ook waar: adolescenten met veel depressieve symptomen bewogen vervolgens minder dan adolescenten met minder depressieve symptomen. Cognitieve symptomen van depressie, zoals verlies van interesse en depressieve stemming, hingen sterker samen met lichamelijke activiteit dan lichamelijke symptomen zoals verlies van eetlust, slaap en energie.

De studie beschreven in *hoofdstuk III* onderzocht de hypothese dat lichamelijke activiteit beschermt tegen het ontstaan van een depressie. Dit werd in kaart gebracht voor een ongeveer 6 jaar durende periode die liep van de adolescentie tot de vroege volwassenheid. Effecten

van de aard, duur, frequentie en intensiteit van beweging werden nagegaan in de analyse. Lichamelijke activiteit voorkwam een eerste episode van depressie niet in deze studie; de hypothese dat vroege lichamelijke activiteit beschermt tegen het ontstaan van een depressie werd dus niet ondersteund.

Hoofdstuk IV betreft de potentiële rol van de zogenaamde plasticiteitsgenen in de (wederkerige) relatie tussen lichamelijke activiteit en depressieve symptomen. De term plasticiteitsgenen verwijst naar genvarianten waarvan bekend is dat ze de activiteit van bepaalde neuromodulators en neurotropische systemen beïnvloeden. Deze systemen, waaronder het serotonerge en dopaminerge systeem, kunnen worden beïnvloed door fysieke activiteit en depressie. Adolescenten met genvarianten waarvan verondersteld wordt dat ze een hoge mate van plasticiteit weerspiegelen lieten geen sterkere (of zwakkere) verbanden tussen depressieve symptomen en lichamelijke inactiviteit zien dan adolescenten zonder deze varianten. Met andere woorden, er werd geen bewijs gevonden dat de voorgestelde genen een directe invloed hadden op de associatie tussen lichamelijke activiteit en depressieve symptomen.

De studie in *hoofdstuk V* onderzocht of adolescenten die deelnamen aan competitieve sporten minder depressieve symptomen hadden en minder depressieve symptomen ontwikkelden in de loop der jaren. Daarnaast testten we de invloed van geslacht en sportcompetentie volgens klasgenoten op de associatie tussen deelname aan competitieve sporten en depressieve symptomen. Zowel jongens als meisjes die deelnamen aan competitieve sporten rapporteerden minder depressieve symptomen, maar lieten geen verschil zien met betrekking tot toekomstige veranderingen in symptoomniveaus. De associatie tussen deelname aan sport en depressieve symptomen werd grotendeels verklaard door sportcompetentie zoals waargenomen door klasgenoten. Dit suggereert dat atletisch competente adolescenten minder depressieve symptomen rapporteren, ongeacht hun deelname aan competitieve sporten.

Hoofdstuk VI betreft de effecten van de relatieve leeftijd van adolescenten in hun schoolklas op verschillende uitkomsten, waaronder depressieve symptomen, veranderingen in depressieve symptomen tijdens de adolescentie en door de docent waargenomen sportcompetentie. Substantiële relatieve leeftijdseffecten werden geobserveerd in relatie tot de kans om zitten te blijven of een jaar over te slaan: adolescenten die relatief jong waren in hun klas hadden een vier keer zo grote kans dat ze een jaar moesten overdoen dan hun relatief oudere klasgenoten; terwijl de relatief oude adolescenten een 20 keer zo grote kans hadden dat ze een klas mochten overslaan. In de subgroep van adolescenten die een jaar moest overdoen hadden de relatief jonge adolescenten minder depressieve symptomen dan relatief oudere leeftijdsgenoten die ook een jaar over moesten doen. De relatieve leeftijdseffecten hadden

geen invloed op de waargenomen sport competentie in zowel de normatieve groep als de subgroep die een jaar bleef zitten.

In het laatste empirische hoofdstuk van het proefschrift, *hoofdstuk VII*, werd de relatie tussen lichamelijke activiteit en stemming in depressieve en niet-depressieve volwassenen onderzocht door middel van een zogenaamde binnen-persoon benadering. Gedurende een maand werden lichamelijke activiteit en affect (positief en negatief) driemaal daags gemeten met een accelerometer en vragenlijsten. We vonden individuele verschillen in zowel de richting als de sterkte van de verbanden. Bijna alle individuen rapporteerden meer positief affect tijdens of onmiddellijk na lichamelijke activiteit (positief cross-sectioneel verband), maar de associatie was niet altijd significant. Er werd echter geen consistente verbetering in negatief affect geobserveerd. De lange-termijn effecten van lichamelijke activiteit op positief en negatief affect varieerde sterk tussen mensen, onafhankelijk van hun depressieve status. Voor sommige personen voorspelde lichamelijke activiteit een verbetering van de stemming over de tijd, maar voor de meerderheid van de deelnemers bestond dit verband niet of was de relatie zelfs omgekeerd.

Samengevat bevestigt dit proefschrift het bestaan van een relatie tussen lichamelijke activiteit en depressieve symptomen, maar het verband is zwak en vertoont forse individuele verschillen. Sommige mensen voelen zich beter na lichamelijke inspanning, terwijl er voor andere personen geen relatie bestaat tussen stemming en activiteit en weer anderen zich juist slechter voelen na lichamelijke inspanning. De redenen voor deze verschillen zijn tot dusver onbekend; en we weten nog niet welke mensen baat kunnen hebben van een actieve leefstijl. Deze kennis is nodig om effectieve gepersonaliseerde interventies voor de behandeling van depressie te ontwikkelen. Tot dusver is het bewijs dat lichamelijke activiteit kan helpen om depressieve symptomen te behandelen relatief zwak. Kortom, meer onderzoek is nodig voordat lichamelijke activiteit kan worden geïmplementeerd als een effectieve strategie voor de behandeling van depressie.

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Nikolaos

About the Author

On the 23rd of June 1981 Nikolaos Stavrakakis was born in Athens, Greece. He finished secondary education at the International Baccalaureate Moraitis school in Athens in 1999. In the same year he started his study in psychology at Reading University in the UK. After he received his bachelor's degree, Nikolaos undertook a master's degree in Neuroscience in Imperial College in London in 2004. There he worked as an internship at the Cyclotron building of Hammersmith hospital in London investigating emotional regulation and the serotonin transporter gene. From the beginning of 2010 until August 2014 Nikolaos has worked on the research presented in this dissertation. Currently, Nikolaos is living in Athens.

List of Publications

Stavrakakis N, de Jonge P, Ormel J, Oldehinkel AJ. “Bidirectional prospective associations between physical activity and depressive symptoms. The TRAILS Study.” *Journal of Adolescent Health* 2012; 50(5):503-8.

Stavrakakis N, Oldehinkel AJ, Nederhof E, Oude Voshaar RC, Verhulst FC, Ormel J, de Jonge P. “Plasticity genes do not modify associations between physical activity and depressive symptoms.” *Health Psychology* 2013; 32(7):785-92.

Stavrakakis N, Roest AM, Verhulst F, Ormel J, de Jonge P, Oldehinkel AJ. “Physical activity and onset of depression in adolescents: A prospective study in the general population cohort TRAILS.” *Journal of Psychiatric Research* 2013; 47(10):1304-8.

Rhodes RA, Murthy NV, Dresnet MA, Selvaraj S, **Stavrakakis N**, Babar S, Cowen PJ, Grasby PM. “Human 5-HT transporter availability predicts amygdala reactivity in vivo.” *Journal of Neuroscience* 2007; 27(34):9233-7.

Submitted or under preparation

Jeronimus BF, **Stavrakakis N**, Veenstra R, Oldehinkel AJ. “Relative Age Effects in Adolescents: The TRAILS study” (under review).

Stavrakakis N, Roest AM, Verhulst FC, Veenstra R, Ormel J, de Jonge P, Oldehinkel AJ. “Competitive sport participation, sport competence and depressive symptoms in adolescent boys and girls” (under preparation).

Stavrakakis N, Booij SH, Roest AM, de Jonge P, Oldehinkel AJ, Bos EH. “The dynamic relationship between physical activity and mood in the daily life of depressed and non-depressed individuals: a within-subject time-series analysis” (under preparation).

Xiaochen L, **Stavrakakis N**, Penninx BW, Bosker FJ, Nolen WA, Boomsma DI, de Geus EJC, Smit JH, Snieder H, Nolte IM, Hartman CA. “Does refining the phenotype improve replication rates? A candidate gene study on Major Depressive Disorder and Chronic Major Depressive Disorder” (under preparation).

Recent TRAILS Dissertations

Some of the work described in this thesis is part of the Tracking Adolescents' Individual Lives Survey (TRAILS) and was performed at the Interdisciplinary Centre Psychopathology and Emotion regulation (ICPE) of the University Medical Centre Groningen (UMCG), University of Groningen, the Netherlands. More information concerning TRAILS and the research within can be found in the dedicated internet site: www.trails.nl

Recent TRAILS theses

Mathyssek, CM (2014). *The development of anxiety symptoms in adolescents*. Supervisors: Prof. dr. F.C. Verhulst, dr. F.V.A. van Oort.

Prince van Leeuwen, AL (2013). *Blunt vulnerabilities. Identifying risks for initiation and continued use of cannabis in a Dutch adolescent population*. Supervisors: Prof. dr. A.C. Huizink, Prof. dr. F.C. Verhulst, dr. H.E. Creemers.

Verboom, CE (2012). *Depression and role functioning. Their relation during adolescence and adulthood*. Supervisors: Prof. dr. J. Ormel, Prof. dr. W.A. Nolen, Prof. dr. B.W.J.H. Pennix, dr. J.J. Sijtsema.

Marsman, H (2013). *HPA-axis, genes and environmental factors in relation to externalizing behaviors*. Supervisors: Prof. dr. J.K. Buitelaar.

Griffith-Lendering, MFH (2013). *Cannabis use, cognitive functioning and behaviour problems*. Supervisors: Prof. dr. H. Swaab, dr. S.C.J. Huijbregts.

Vink, NM (2013). *The role of stress in the etiology of asthma*. Supervisors: Prof. dr. H.M. Boezen, Prof. dr. J.G.M. Rosmalen, Prof. dr. D.S. Postma.

Laceulle, OM (2013). *Programming effects of adversity on adolescent adaptive capacity*. Supervisors: Prof. dr. J. Ormel, Prof. dr. M.A.G. van Aken, dr. E. Nederhof.