Development of overweight in adolescence

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Chapter 6

Summary & General Discussion

In this thesis we evaluated various factors in childhood that may predict overweight in adolescence. Additionally, we compared and validated various measurement methods of overall and abdominal adiposity in children. In this last chapter, we will summarize our findings and integrate them. We will discuss public health implications, limitations and methodological issues, and offer directions for future research.

SUMMARY

Definitions of overweight and obesity are based on the BMI, which is calculated as weight (in kg) divided by height squared (in m^2) (**chapter 1**). For children, age- and sex-specific cut-off values have been developed based on an international survey.[1] Based on these cut-off values, the prevalences of overweight and obesity in children have increased dramatically across the Western world in the past three decades.[2-4] Although recently this increase seemed to level off, the number of overweight children worldwide is staggering.[5-9] These increased prevalences have major public health implications, most importantly because of tracking of overweight into adulthood which leads to cardiovascular morbidity and mortality. Social changes such as increased portion sizes and use of motorized transport underlie the increased prevalence of overweight. On the individual level, predictors for childhood overweight comprise genetic variation, social factors, dietary factors, behavioral and psychological factors, amount of physical and sedentary activities, and accelerated growth in certain periods in life.

In this thesis we focused on risk factors for overweight at the individual level. We investigated several predictors for the development of overweight in adolescence. These were evaluated in our study cohort as part of the TRAILS study, an ongoing population-based cohort study assessing psychosocial and physical health from age 10 to age 24 years. Three assessment visits have been performed in 2001-2002, 2003-2004 and 2005-2007, at mean ± SD ages of 11.1 ± 0.6, 13.5 ± 0.6, and 16.2 ± 0.7 years, respectively.

Genetic background predicts an individual's susceptibility to weight change due to a certain lifestyle.[10,11] Multiple genes are involved, probably interacting with each other and with environmental factors, implying a multifactorial trait. Recently, genome wide association studies (GWASs) in large cohorts have identified common variants associated with overweight, specifically variants near *INSIG2*, in *FTO* and near *MC4R*. In line with other large studies,[12-15] we do not find associations with the SNP near *INSIG2* in data from the TRAILS population (**chapter 2.1**). This supports the hypothesis that an important role for *INSIG2* in the etiology of childhood overweight is unlikely. In contrast, we find that common variation in the *FTO* gene is associated with overall and abdominal adiposity and fasting glucose. Variation near the *MC4R* gene is associated with BMI. The associations are

stable between ages 11 and 16 years. These findings strengthen and extend the results from previous research.

Genetic variation might exert part of its influence through variation in increased energy intake.[11,16] Apart from appetite and satiety, impulsivity might have a role in the development of overweight.[17] For example, lack of self-regulation has been associated with faster childhood weight gain.[18] Research regarding genetic variation underlying impulsivity has focused mainly on the dopaminergic and serotonergic systems.[19-25] We aimed to assess the influence of common variation near the dopaminergic *DRD2* gene and in the *serotonin transporter* (*SLC6A4*) gene on the association between impulsivity and adiposity (**chapter 2.2**). Specifically, we aimed to evaluate whether this genetic variation exerts its influence on adolescent adiposity via impulsive personality characteristics. Our results support an association between impulsivity and measures of overall and abdominal adiposity. We do not find evidence for associations between genetic variation near the *DRD2* gene and in the *SLC6A4* gene and impulsivity; nor for associations between variation near the *DRD2* gene and in the *SLC6A4* gene and adiposity measures.

It has been reported that critical time periods exist in which accelerated growth constitutes a risk factor for subsequent adiposity and its associated metabolic complications.[26] It is unclear which of these age periods is most important for overall and abdominal adiposity in adolescence. We evaluated the influence of changes in weight and BMI SDS between birth and age 15 years on adolescent overweight (**chapter 3**). Increases in weight SDS, especially between 2 and 7 years, predispose to overall and abdominal adiposity in adolescence. In adolescents whose mothers smoked during pregnancy, the influence of weight gain during these years is more pronounced.

It is known that both overweight and depressive problems are common in adolescence. Recent studies suggest a longitudinal association in which depressive symptoms in childhood and adolescence precede overweight in later life.[27] We systematically reviewed the literature concerning the association between childhood and adolescent depression and subsequent overweight (**chapter 4.1**). Most cross-sectional and longitudinal research satisfying our quality criteria supports an association between depressive symptoms in childhood and adolescence and subsequent overweight. However, no studies evaluated the influence of depressive symptoms on various measurements of overall and abdominal fat and associated metabolic characteristics in adolescence. In our data from the TRAILS population, we find that depressive problems at age 11.1 years are associated with increased overall and abdominal adiposity at age 16.2 years (**chapter 4.2**). They do not predict increases in BMI or sum of skinfolds over time, suggesting that the association between depressive problems and BMI remains stable during adolescence. Persistent depressive problems are associated with increased BMI and risk of overweight.

The second part of this thesis consists of two studies which focus on measurements of body composition in prepubertal children. Although BMI is easy to obtain and very

reliable, it does not differentiate between lean body mass and fat mass. The most valid measures for total body fat are multicompartment models, underwater weighing, doubly labeled water, and dual-energy X-ray absorptiometry; and for abdominal fat, CT and MRI.[28] However, these methods are not suitable for large epidemiological studies because of high costs and limited accessibility.

We compared various measurements of total body fat in 17 boys and 13 girls aged 6 to 7 years. Body fat was assessed using the reference methods isotope dilution and DEXA. Skinfold thicknesses, BIA, weight and BMI were compared with these reference methods (**chapter 5.1**). The tested methods result in rather different absolute values for total body fat. We conclude that noninvasive methods are presently not suited to assess the absolute amount of total body fat in 6-7-year-old children. In the same population of prepubertal children, we estimated abdominal fat with the use of anthropometry, DEXA, and ultrasound, and compared these estimates with amounts determined by CT (**chapter 5.2**). Our results suggest that skinfold measurements are the best noninvasive technique in predicting subcutaneous as well as intra-abdominal fat in prepubertal children. Our findings from chapter 5.1 might seem contradictory to the findings in chapter 5.2. However, in chapter 5.2 we take a slightly different approach by assessing prediction of absolute values of abdominal fat. Therefore, we can conclude that although determination of absolute values or ranking is not possible for non-invasive methods, they can be used to predict amounts of fat.

DISCUSSION

Genes

In our population study, variation near the *MC4R* and particularly in the *FTO* gene shows a clear association with overweight measures in adolescence, but effect sizes and explained variances are small (Table 1). The two genes were independently related to the adiposity measures and together they explain 0.007 to 0.010 of the variance in BMI, sum of skinfolds, %BF, and waist circumference. These two genes were previously identified in GWASs. Such studies in large populations have currently identified variants which together explain approximately 2%[29] of all phenotypic variation in adults, and 1.12% of variation in children.[30] In contrast, the total variance explained by genetic factors, i.e. the 'heritability' has been estimated at 30 to 70% according to family-based studies.[10,11] The presently unidentified or 'missing' heritability could have several sources.[31] Most GWASs were performed in populations of European ancestry, which contain less genetic variation compared with populations of recent African ancestry. In addition, GWASs are based on the 'common disease, common variant' hypothesis stating that common diseases are influenced by a few common variants with relatively small effect sizes; and not by a large number of rarer variations.[32] These studies have therefore been designed to investigate only genetic vari-

ants with a MAF of at least 5%. However, rarer variants have been described to influence severe obesity.[33] These variants could show relatively large effect sizes and consequently explain a substantial part of the heritability.[31] Moreover, precision of the current heritability estimates is hampered by other sources of family resemblance such as shared family environment, nonadditive genetic effects, and gene-gene and gene-environment interactions. Finally, other forms of genetic variation that were not investigated in GWASs, such as copy number variants (insertions or deletions) and copy neutral variations (inversions or translocations), could account for part of the missing heritability. As rapid changes are occurring in the field of genetics of complex diseases, i.e. development of more extensive and less expensive arrays and different analysis methods, opportunities will increase to find other and rarer forms of genetic variation.

Genetic variation does not change rapidly throughout generations. It can therefore be questioned how genetic influences have an important role while the prevalence of overweight has increased over the past three decades. Clearly, gene-environment interaction is the answer, but how does this occur? Various hypotheses have been formulated to explain the genetic influence on the obesity epidemic.[32]

1. The thrifty gene hypothesis: this hypothesis states that in view of scarcity in the past, evolution has favored the ability to increase weight by means of increased reproductive fitness. Food has become more abundant, which could have led to increased prevalences of overweight and obesity. The fact that this increase in prevalences started in the Western world and is currently also becoming a problem in developing countries,[34] supports this hypothesis. The higher prevalences among e.g. Pima Indians and Hispanic-Americans in the United States also suggest that thrifty genes might have a role in the obesity epidemic. However, specific genes have not been identified in these populations.
2. The predation release hypothesis: this hypothesis disputes the thrifty gene hypothesis, arguing that famine could not have provided sufficient force to drive evolution towards an obesity prone phenotype.[35,36] Instead, the need to escape from possible predators might have prevented humans from becoming overweight in the past.[35,36] Development of better protective strategies could have caused 'predation release' and consequently an increased risk of overweight. This hypothesis does not assume that overweight was advantageous during evolution, but rather supposes that overweight genes were randomly passed on across generations. This hypothesis is supported by reports that the overweight epidemic is leveling off.[7,35]
3. The dietary shift hypothesis: this hypothesis concurs with the predation release hypothesis assuming that overweight genes have not been positively selected across evolution. Historically, humans have never been exposed to high amounts of dietary fat. Genetic variation resulting in impaired fat oxidation could have evolved from harmless to detrimental as diets changed.[36] These last two hypotheses are contradicted by the

fact that deleterious genetic variants associated with an increased risk of overweight and type 2 diabetes are more frequent than can be explained by random mutation.[37]

4. The fetal programming hypothesis: intra-uterine environment is thought to be important for the development of overweight in later life. This could be related to epigenetic mechanisms which occur when gene expression is altered by methylation of promoter binding sites, modifications in histone proteins that alter binding sites, or involvement of noncoding RNA's (ribonucleic acids).[38,39] By causing permanent alteration of gene expression these epigenetic phenomena, which might also be heritable, can lead to increased susceptibility to overweight across generations.
5. The ethnic shift hypothesis: different risk of overweight across ethic groups[5,40] might be because of genetic variation. However, no genes have been identified that were specific to certain ethnic populations.
6. The assortive mating hypothesis: assortive mating denotes nonrandom mating based on certain phenotypic or cultural characteristics, e.g. overweight. This hypothesis is supported by the low albeit significant correlation between BMIs of spouses.[41,42] Assortive mating could lead to increases in homozygosity for genetic polymorphisms associated with overweight risk and consequently have a role in the overweight epidemic.[43] The fact that increases in leanness have not been reported might be because of the heterogeneity in the origin of leanness. Leanness is probably not associated with a specific genotype.[42] Lean populations constitute people who have not been exposed but do have a genetic predisposition to develop overweight and people who do not.[42]

It is very plausible that not just one mechanism exists through which genetic variation influences the increased prevalence of overweight.[32] This would suit the complex etiology of overweight, but does not provide direction to further research, not to mention prevention or treatment. Although discussion on these various hypotheses is interesting from a theoretical point of view, from a pragmatic point of view the hypotheses on dietary shift and fetal programming are most interesting because these factors might be influenced. Additionally, evaluation of the thrifty gene and ethnic shift hypotheses could be interesting in tailoring preventive and therapeutic strategies to various subgroups.

Growth

When we compare explained variances and effect sizes of the associations between all evaluated predictors and measures of overweight, weight gain between 2 to 4 years and 4 to 7 years appears to show the strongest association (Table 1). Although weight gain above average must have taken place in the years before adolescence, the strong associations for weight gain during the age periods between 2 and 7 years are remarkable. Research on critical time periods for the development of overweight is important with regard to effective timing of preventive strategies.

Table 1. Effect sizes of associations between various determinants and adolescent overweight.

Predictor	N	BMI[1]	Sum of skinfolds[1,2]	Body fat %[1]	Waist circumference[1]	Overweight (including obesity)[3]
FTO (rs9939609)	1173	0.006 0.11 (0.03 – 0.19)	0.007 0.12 (0.04 – 0.20)	0.006 0.11 (0.03 – 0.19)	0.006 0.11 (0.03 – 0.19)	1.34 (1.06 – 1.69)
MC4R (rs17782313)	1173	0.005 0.11 (0.02 – 0.20)	0.001 0.05 (-0.04 – 0.14)	0.001 0.04 (-0.05 – 0.14)	0.002 0.07 (-0.02 – 0.16)	1.20 (0.93 – 1.54)
Impulsivity	1212	0.005 0.02 (0.003-0.03)	0.002 0.01 (-0.004-0.03)	0.004 0.02 (0.001-0.03)	0.005 0.02 (0.004-0.04)	1.04 (0.99 – 1.09)
Weight gain 2-4 yrs	1480	0.145 1.47 (1.32 - 1.63)	0.101 1.24 (1.07 – 1.42)	0.113 1.30 (1.12 – 1.48)	0.112 1.30 (1.12 – 1.48)	35.7 (18.0 – 70.9)
Weight gain 4-7 yrs	1480	0.089 1.11 (0.97 – 1.25)	0.083 1.08 (0.92 – 1.24)	0.101 1.18 (1.02 – 1.34)	0.048 0.82 (0.57 – 0.96)	24.8 (12.7 – 48.2)
Depressive problems	1520	0.004 0.20 (0.04 – 0.36)	0.002 0.15 (-0.01 – 0.30)	0.010 0.31 (0.15 – 0.47)	0.004 0.19 (0.03 – 0.35)	1.79 (1.21 – 2.67)

[1] Explained variance, regression coefficient (95% confidence interval) reported from linear regression analyses using within population calculated SDSs as outcome measures.

[2] Ln-transformed before calculation of SDSs to obtain a better approximation of the normal distribution.

[3] Odds ratios are reported from logistic regression analyses using the international age- and sex-adjusted BMI criteria to define overweight and obesity

Growth in critical time periods gained interest in obesity research because results from the Dutch Hunger Winter studies showed that men who had been exposed to maternal undernutrition in the first trimester of pregnancy had an increased risk of obesity, whereas exposure during the third trimester was associated with a decreased risk.[44] In 1990, Barker formulated his 'fetal origins of health and disease hypothesis'.[45] This hypothesis states that risk of overweight is 'programmed' during fetal and infant life. Programming was defined by Lucas as 'a more general process whereby a stimulus or insult at a critical period of development has lasting or lifelong significance'.[46] Both undernutrition in utero and postnatal catch-up growth have been suggested as possible insults in critical periods, which could lead to increased risk of overweight and its metabolic complications in later life. Undernutrion in utero could influence the fetus to be prepared for food scarcity post-natally. Catch-up growth preferentially leads to increased fat mass.[47,48]

Various pathways could be involved in the permanent influence of insults during these critical periods, such as hormonal axes, modification of metabolic rate, regulation of appetite and physical activity, and proliferation and differentiation of fat cell precursors.[48,49] Undernutrition in utero and subsequent catch-up growth could 'program' permanent modifications to abovementioned processes and consequently result in increased risk for overweight. These mechanisms might have an important role in case of fetal growth restriction and therefore might be important for a subgroup of overweight children.

We evaluated data from a population-based cohort of children with a large range in birth weights. Our findings suggest that growth between 2 to 4 and 4 to 7 years is most important. This concurs with the adiposity rebound, a term proposed by Rolland-Cachera to describe the nadir in BMI.[50] After an initial rise until age 1 year, BMI decreases to a nadir between ages 3 to 7 years before it starts to rise again. It has been reported that timing of the adiposity rebound is associated to subsequent overweight, independent of BMI at the start of the adiposity rebound.[51,52] It was shown that the increase in BMI is because of increased weight gain rather than slower gain in height.[52] The increase in weight is almost completely determined by an increase in body fat as determined by DEXA.[53] Adiposity rebound has been criticized as an 'epiphenomenon' or 'statistical finding'.[54] Early age at adiposity rebound might only reflect upward centile crossing. Insofar as upward centile crossing at this age seems to be important for subsequent overweight, these studies remain in line with our findings.

Mood

Although we found small effect sizes for depressive problems in childhood, they seem to explain a larger part of the variance in adiposity measures than the genetic risk factors (Table 1). As Blaine and colleagues wrote regarding the odds ratio of 1.47 they found in a meta-analysis of longitudinal studies on depression and adult overweight: '*To put this*

effect in context, the effect of adolescent depression on obesity in the young adult is larger in size than the effect of passive smoking on the development of cancers.'[55]

Several causal pathways linking depressive problems in childhood and adolescent overweight can be hypothesized such as use of anti-depressants, decreased physical activity, and increased appetite. Not many adolescents in our study population used anti-depressants (n=3), which can therefore not explain the association we found. Physical activity has been included in a few studies, but no evidence for mediation was found.[56-59] We obtained similar findings from additional analyses, with the use of a questionnaire on physical activity. We found that depressive problems and physical activity were independently related to overweight measures (data not shown). Increased appetite has been described as a symptom of atypical depression.[60] Central serotonergic pathways have been implicated in disturbances in mood and appetite.[56,61] It is hypothesized that in susceptible individuals, brain serotonin increases by ingestion of carbohydrate rich foods, and thereby positively affecting mood.[61] In case of depressive mood, appetite control and maintenance of body weight might be sacrificed over improvement in mood, favoring ingestion of carbohydrate rich foods.

Evidence has also been found for a reverse hypothesis of overweight causing depression.[62,63] In data from our population, analyses on the reverse association between adiposity and depressive symptoms provided weaker, nonsignificant results (data not shown). Nevertheless, it is possible that the association between depressive symptoms and overweight is characterized by a 'lifelong reciprocal nature' of influencing each other, as postulated by Pulkki-Råback and colleagues regarding the association between depressive symptoms and the metabolic syndrome.[64] Findings from a prospective study among American adolescents support this hypothesis.[63,65]

Another explanation for the association between depressive symptoms and adiposity is the existence of a third factor that causes both depressive problems and overweight, albeit at different periods of life. Specifically, genetic variation and/or programming in utero determining development of HPA axis and serotonerg systems could influence both depressive problems and overweight. Various studies suggest that both depressive symptoms and overweight are related to a dysregulation of the HPA axis.[66] Elevated cortisol levels have been associated with both depressive symptoms[67] and overweight,[68] more specifically with increased visceral fat storage and increased energy intake. The observations that both depressive symptoms and overweight are associated with increased HPA axis activation could be owing to a common etiology.

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

Genes

Direct public health implications from genetic studies are limited. Small explained variances prohibit the use of genetic testing as screening instruments. However, unravelment of etiological pathways could lead to more suitably tailored preventive programs. Research on genetic variation underlying overweight is important, mainly to gain understanding of the pathophysiologic mechanisms implicated in the development of overweight. Increased knowledge on pathophysiology could improve effectiveness of preventive and therapeutic strategies.

FTO has been implicated in increased food intake[69,70] and decreased satiety[71] but not in energy expenditure.[69,70] This is in contrast to findings from a study in *FTO* deficient mice in which higher energy expenditure was found in the presence of relative hyperphagia.[72] *MC4R* was associated with higher total energy, fat, and protein intake was found in middle-aged women.[73] These findings are in line with the influence of rare *MC4R* mutations on energy intake.[74] In a family-based study among Hispanic-American children, multiple genetic variants of *MC4R* were related to energy intake, but even stronger to energy expenditure.[75] Taken together, these findings suggest a dual influence of *MC4R*.

Further unravelment of pathways involved in these mechanisms through molecular and physiogical studies is the starting point for development of better tailored prevention and treatment. Direct improvements from e.g. leptin treatment in leptin deficient overweight patients cannot be expected because of the multifactorial nature of common overweight. However, pathophysiologic studies could direct clinical trials in determining if certain subgroups would benefit from focusing more on energy intake or energy expenditure. Results from a recent study evaluating a nutritional and lifestyle prevention program from the age of 8 months suggested that the intervention was not intense enough to abolish the effect of the *FTO* polymorphism on BMI at age 15 years.[76] This implies that certain genetic characteristics predispose to a vulnerability which is not easily eliminated by general preventive strategies on healthy nutrition and lifestyle.

Growth

Since weight gain from 2 to 7 years appears to very be important in the development of overweight, preventive strategies should commence at or before the age of 2 years. Our finding that smoking during pregnancy aggravates the influence of weight gain from 2 to 7 years, might provide an opportunity for prevention. Preventive strategies that focus on high risk groups should especially target children whose mothers smoked during pregnancy. Additionally, in view of all adverse effects on health, of course, smoking should be discouraged.

The US Preventive Services Task Force (USPSTF) recommends clinicians to screen children aged 6 years and older for obesity and subsequently refer them for intervention programs.[77] However, at present, population screening for development of overweight does not seem justified. The World Health Organization defined criteria for justification of screening programs.[78]

1. The condition is an important health problem for both individual and community.
2. There is an accepted treatment or useful intervention for the condition; treatment at an early stage will lead to a better prognosis than treatment at a later stage.
3. Facilities for diagnosis and treatment are available.
4. The condition starts with a recognizable latent or early asymptomatic phase.
5. A valid and reliable screening instrument exists.
6. The screening instrument is acceptable to the population.
7. The natural history of the condition, including the latent phase, is adequately understood.
8. Consensus exists on whom to treat.
9. The cost of screening is balanced against the economic burden of the disease.
10. Case finding should be a continuous process.

There is no doubt that overweight constitutes an important health problem with a huge economic burden of disease (1,9). Facilities for diagnosis and preventive treatment are present, at least in the Netherlands. Well-child clinics and school health services provide excellent opportunities to reach the majority of the population in a continuous program (3,10). However, evidence for effective prevention and treatment programs remains scarce (2).[79] Moreover, no consensus exists on the most appropriate screening tool (5).[79] Overweight and obesity are arbitrarily defined based on BMI, but its predictive value for future morbidity (7), especially in comparison with measures of body fat, still needs to be established. This also raises questions on whom to treat (8). Importantly, potential harms of screening (i.e. stigmatization) are understudied.[79] This is in conflict with the 'primum non nocere' principle, i.e. avoiding harm at all costs, which is the basic rule of all medical care. The USPSTF assumes that harms of screening are minimal, but does not provide support for this assumption.[77] In the evidence synthesis underlying the recommendations of the USPSTF it is admitted that evidence lacks for both the potential harms of screening and for BMI as a screening tool.

Mood

Although the nature of the association between depressive problems and overweight is currently unknown, we could tentatively draw some conclusions on public health implications, based on our findings and those of others. Treatment programs for childhood depression should consider that depressive problems might be followed by increases in body weight. Treatment programs should be adapted to include prevention and treatment

of overweight. On the other hand, in treating overweight individuals, it should be kept in mind that depressive symptoms could underlie the increase in body mass. Assessment of depressive symptoms and binge eating warrants consideration, especially if overweight treatment fails. In pediatric primary care it is important to maintain a dialogue with children and parents regarding both mental health and overweight. In this dialogue, it is important to be sensitive to social context and feelings of guilt that parents might have.[80]

Comorbidities of childhood overweight

Already in childhood, overweight is associated with development of the metabolic syndrome, which consists of a cluster of cardiovascular risk factors. The IDF defined age-adjusted criteria for the metabolic syndrome based on abdominal obesity, dyslipidemia, glucose intolerance and hypertension.[81,82] The prevalence of the metabolic syndrome is increased in overweight children. Although the existence of exact cut-off values for normal versus pathological remain controversial, it is evident that abnormalities in the components of the metabolic syndrome already start in childhood.[83]

We evaluated the influence of several predictors on SBP, triglycerides, HDL, LDL, glucose, insulin, a composite metabolic syndrome score,[84] and presence of the metabolic syndrome according to the IDF criteria. We found that genetic variation in the *FTO* gene was associated with an increased risk of the metabolic syndrome of 2.05 (p=0.003). Adjustment for BMI in this association resulted in a nonsignificant OR of 1.66 (p=0.09), which suggests that the effect of FTO variation on the presence of the metabolic syndrome was mediated by BMI. In addition, weight gains between age 2 to 4 and 4 to 7 years were also associated with higher SBP, insulin, LDLC, triglycerides, and metabolic syndrome score (+0.31 to +0.73 SD); and with lower HDL (-0.24 to -0.28 SD). Gains in the age period between 11 and 15 years were also associated with large increases in explained variance of these metabolic traits. After adjustment for current BMI SDS, estimates for all metabolic traits were substantially reduced to nonsignificant effects. Finally, depressive problems at age 11.1 years were associated with a significantly lower HDLC at age 16.2 years. Adjustment for BMI did not attenuate the association (B=-0.09; 95% CI, -0.14 – -0.03). No significant associations were found with the other metabolic characteristics or with the composite metabolic syndrome score.

In conclusion, several predictors for childhood overweight were also associated with the metabolic syndrome or components of the metabolic syndrome. These associations were mostly mediated by BMI.

LIMITATIONS AND METHODOLOGICAL ISSUES

Genes

Because of the small effects genetic variants have on overweight, sample sizes in which these associations are studied need to be large. Our sample size was large enough to detect main effects, but limited for the evaluation of interaction effects of e.g. physical activity. It has been estimated that a population of at least 150.000 individuals is required to detect gene-environment interactions.[85] However, detailed phenotyping increases power to detect effects and would be able to reduce the required sample size to 10.000.[85]

We found no influence of genetic variation in the *DRD2* and *SLC6A4* genes on impulsivity and adiposity measures. This was not completely surprising in view of the limited prior evidence we found for an association of these genes with impulsivity and overweight, in contrast to the stronger evidence from GWASs for the influence of *FTO* and *MC4R* on overweight.

Growth

As mentioned previously, it is statistically difficult to identify critical periods of growth because growth in almost all periods shows statistically significant correlation (absolute Pearson's correlation coefficients ranging from 0.05 to 0.85, p-values 0.01 to <0.001). This has led to various strategies for the analysis of longitudinal observational data.[86,87] Stettler introduced the life-course plot which visualizes effect sizes from logistic regression analyses (weight gain in various age periods as determinants of adult overweight), plotted against age.[86] Large increases in effect size in a certain age period would signify importance of weight gain in this age period for adult overweight. Keijzer-Veen and colleagues propose to use a regression model with unexplained residuals to assess the influence of two correlated predictors on outcome measures in later life.[87] We looked at increases in explained variances in regression analyses of weight gain on continuous overweight measures, which is comparable to Stettler's life-course plots. However, we adjusted effect sizes only for current weight, whereas Stettler also adjusted for weight gain in other age periods. It remains debatable which of these methods describes the actual situation best. Hypothetically, only randomized controlled intervention studies would be able to distinguish the influences of weight gain during different age periods. However, such studies are not feasible, at least not in humans.

Another point of discussion is the use of standardized weight scores derived from cross-sectional studies in longitudinal analyses. It has been shown that the use of standardized scores to describe longitudinal data decreases power to detect statistically significant effects.[88,89] This might be owing to the fact that higher centiles are further apart, thus attenuating change and variability in fatter children. This issue also raises questions on how growth is monitored best, i.e. by standardized or nonstandardized measures.

Mood

No gold standard exist for the measurement of depressive symptoms in childhood. Two main approaches are widely used: the clinical-diagnostic approach and the empirical-quantative approach. In the first, a 'top down' approach, a certain set of features as described by experts is used to determine whether depression is present. In the latter, a 'bottom up' approach, criteria for depression are derived from symptoms that generally occur in children. The CBCL questionnaire, filled out by parents and the YSR, filled out by children we used, are examples of the latter approach. However, we used DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV) constructs derived from these scales to determine a continuous depressive symptoms score.[90] Comparison of the DSM-IV construct score with the top-down Revised Child Anxiety and Depression Scale (RCADS) shows good correlation.[91]

For our analyses, the continuous depressive symptoms score was standardized for boys and girls separately, and a mean of the parent and child standardized scores was used as a measure of depressive symptoms. This score was subsequently dichotomized using a cut-off of 1.04 (sex-specific 85th percentile), creating a subgroup with 'depressive problems' to allow for comparison with other studies in which such cut-offs were used. With regard to this approach, several limitations need to be addressed. First, we combined data from parent and child reports. Although this has been described as less vulnerable to context and perspective,[92-94] other have advised against it because agreement was low and no clear advantages were found by the use of multiple informants.[95] Second, we used an arbitrary cut-off value. Although repeated analyses using 82nd and 88th percentile cut-offs showed similar results, others have used the 97.5th percentile to define clinical cases.[96] This was not possible in our analyses because it would have made subgroups too small. Finally, we used sex-specific cut-off values which assumes that equal amounts of depressive symptoms are present in boys and girls. Although this assumption can be questioned, the use of a general cut-off value also has its disadvantages, because it would imply calculation of standardized scores for the whole group whereas means are very different for boys and girls. Future results from the TRAILS study, which will evaluate depressive symptoms from age 10 to age 24 years, might improve knowledge on cut-off values with clinical relevance, especially with respect to subsequent depressive disorder.

In general, we have described several risk factors for overweight in adolescence in association studies with the use of data from a large population-based cohort, which also has its limitations in terms of measurement error and loss to follow-up. Moreover, it is tempting to draw causative conclusions, although strictly, this is not possible in our association studies.

DIRECTIONS FOR FUTURE RESEARCH

Many different risk factors influence overweight. Rapid weight gain between ages 2 to 7 years seems to be important. This does not imply that earlier weight gain is not important. Infant weight gain could lead to an earlier adiposity rebound. Together with other factors such as genetic, behavioral and social characteristics, it could influence growth between age 2 and 7 years and consequently lead to overweight in adolescence. It would also be interesting to evaluate whether depressive problems have a role in this pathway. In summary, various pathways can be hypothesized (Figure 1). It is not possible to include all information, including repeated measures of growth, in regression analyses. More advanced statistical methods are being developed, which could evaluate these hypothesized pathways. Path analysis is a form of structural equation modeling in which the goodness of fit of a theoretical pathway is established.[97,98] Multiple theoretical pathways or frameworks can be defined a priori and compared to establish which pathway fits the current data best. Testing of pathways including various biological, psychological, and social factors is in line with the life-course approach which various researchers have advocated.[98,99]

Focusing on the predictors described in this thesis, several specific research questions and directions require attention.

Genes

Focus in genetic association studies should be on research in non-European samples, more precise phenotyping, and measurement of environmental exposures in search of gene-environment interaction.[31] The search for rarer variants is also important, as illustrated by results from a resequencing study in Hispanic-Americans which suggest that the influence

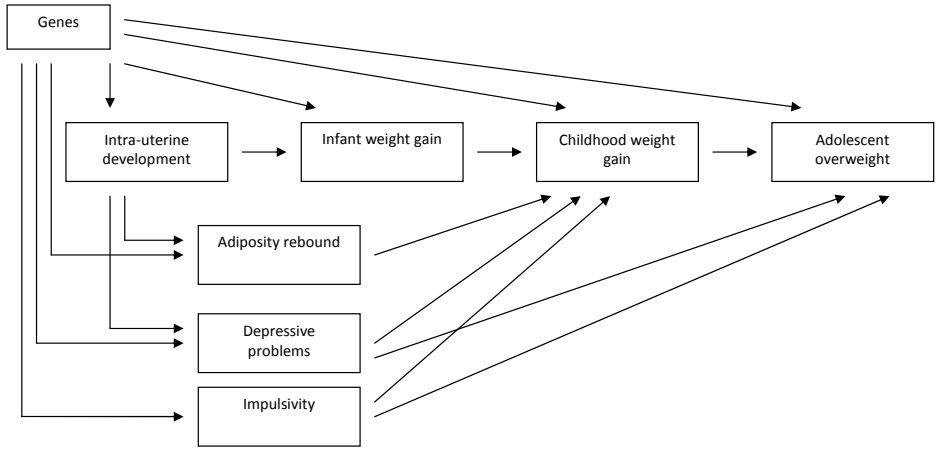

Figure 1. Pathways to development of overweight in adolescence.

of MC4R on overweight is more likely owing to multiple rare variants than few common variants.[75] The search for rarer variants in population-based studies requires very large sample sizes and thus extensive collaboration. Studies in isolated populations and family based or case-control studies might be necessary to uncover rare variants.

Laboratory research is needed to address questions regarding epigenetic mechanisms. As James Watson stated: '*The major problem, I think, is chromatin… you can inherit something beyond the DNA sequence. That's where the real excitement of genetics is right now.*[100] Epigenetic mechanisms determine gene-expression, but many questions remain to be elucidated: how are these factors inherited throughout cell divisions? How is it possible that these mechanisms are consistent throughout cell division but flexible in influencing gene expression? How are histone modifications inherited? Which are the precise molecular mechanisms?

Growth & body composition

As described above, growth could be modeled with the use of path analysis. Specifically, studies should focus on what determines accelerated growth between age 2 and 7 years. Are perinatal programming mechanisms involved? Possible advantages of accelerated growth, for example on neurodevelopment should also be explored.

Various noninvasive simple measurements should be studied longitudinally to determine their consequences for cardiovascular risk in adulthood, and to be able to determine the effectiveness of prevention programs. In addition to BMI, skinfolds and waist circumferences should be obtained regularly in formal monitoring programs at well-child clinics and schools.[28] Monitoring of growth in childhood, not only through BMI but also through skinfolds and waist circumference, is an important start point to develop suitable screening programs. This would also provide longitudinal growth standards according to which standardized scores can be calculated. Longitudinally derived standardized scores are better suited in longitudinal studies that evaluate predictors for overweight.[84]

These ideas might seem to contradict our findings from chapter 5.1, in which we conclude that simple non-invasive measures are not suitable for measurement of total body fat. However, in chapter 5.2 we take a slightly different approach by assessing prediction of absolute values of abdominal fat. From this latter study, we conclude that non-invasive measurements of skinfold thicknesses and waist circumference do predict abdominal fat. Therefore, we can conclude that although determination of absolute values or ranking is not possible for non-invasive methods, they can be used to predict amounts of fat. This implies their potential benefit to monitoring programs.

Mood

Validation of feasible measures for depressive symptoms in childhood, especially development of cut-off values associated with clinically relevant symptoms, is important. In ad-

dition, the association between depression and overweight should be explored. Common determinants, such as genetic variation and intra-uterine programming can be explored in the abovementioned path analyses.

To conclude, what impact will research on predictors for overweight have? Important predictors derived from observational studies could be incorporated in preventive intervention studies. These interventions studies should be monitored or evaluated in a randomized controlled design to determine which risk factors can be influenced. By influencing these risk factors we hope to not only stabilize, but also reduce the prevalence of overweight in childhood and its associated complications.

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