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**Abbreviated title:** Shared familial risk factors between ADHD and overweight/obesity

**Conflict of interest:** In the past year, Dr. Faraone received income, potential income, travel expenses and/or research support from Rhodes, Arbor, Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, NeuroLifeSciences and NACE. With his institution, he has US patent US20130217707 A1 for the use of

sodium-hydrogen exchange inhibitors in the treatment of ADHD. He is principal investigator of www.adhdinadults.com.

Dr. Cortese has received royalties from Aargon Healthcare Italy from 2010 to 2014. He has received grant or research support from the Solent National Health Service (NHS) Trust, UK. He has received honorarium and travel expenses from the Association for Child and Adolescent Mental Health (ACAMH), UK.

Dr. Larsson has served as a speaker for Eli-Lilly and has received a research grant from Shire; both outside the submitted work.

The other authors declare no conflicts of interest.

**Abstract**

**Background:** Despite meta-analytic evidence for the association between attention-deficit/hyperactivity disorder (ADHD) and overweight/obesity, the mechanisms underlying the association are yet to be fully understood.

**Methods:** By linking multiple Swedish national and regional registers, we identified 472 735 index males born during 1973–1992, with information on body weight and height directly measured before they were conscripted for military service. We further identified 523 237 full siblings born during 1973–2002 for the index males. All individuals were followed up from their third birthday to December 31, 2009 for ADHD diagnosis. Logistic regression models were used to estimate the association between overweight/obesity in index males and ADHD in their full siblings.

**Results:** Siblings of index males with overweight/obesity had increased risk for ADHD (Overweight: OR=1.14, 95% CI=1.05–1.24; Obesity: OR=1.42, 95% CI=1.24–1.63), compared with siblings of index males with normal weight. The results were adjusted for birth year of the index male and sex of the sibling. After further adjustment for ADHD status of the index male, the familial co-aggregation remained significant (Overweight: OR=1.13, 95% CI=1.04–1.22; Obesity: OR=1.38, 95% CI=1.21–1.57). The results were similar across sex of the siblings.

**Conclusions:** ADHD and overweight/obesity share familial risk factors, which are not limited to those causing overweight/obesity through the mediation of ADHD. Future research aiming at identifying family-wide environmental risk factors as well as common pleiotropic genetic variants contributing to both traits is warranted.

**Keywords:** ADHD; Obesity; Family factors; Genetics

## Introduction

The worldwide prevalence of attention-deficit/hyperactivity disorder (ADHD) is estimated to be 3.4–7.2% in children and adolescents (Polanczyk et al., 2015, Thomas et al., 2015) and 2.5–3.4% in adults (Fayyad et al., 2007, Simon et al., 2009). ADHD is associated with increased risk of severe adverse outcomes in multiple domains, resulting in substantial negative influence on affected individuals, their families, and society at large (Chorozoglou et al., 2015).

During the last few decades, many countries have documented an increase in the body mass index (BMI) of their populations (Neovius et al., 2006, Neovius et al., 2013, Wang and Beydoun, 2007). The prevalence of obesity in adults has been estimated to be more than 10% in Sweden (Neovius et al., 2013) and 34.9% in the United States (Ogden et al., 2014). Given its adverse impact on health and quality of life, obesity imposes considerable economic burden to individuals and public health systems (Muller-Riemenschneider et al., 2008).

Despite meta-analytic evidence for the association between ADHD and obesity both in children/adolescents [odds ratio (OR): 1.20] and adults (OR: 1.55) (Cortese et al., 2015), the mechanisms underlying the association are yet to be fully understood. The impulsive and inattentive components of ADHD might have direct effects on obesity through the mediation of disordered eating patterns and poor planning, respectively (Cortese and Castellanos, 2014). Comorbid psychiatric conditions, such as depression, anxiety, and substance use disorder, might act as confounders and to some extent account for the association between ADHD and obesity (Luppino et al., 2010, Gariepy et al., 2010, Cortese et al., 2015). Given that both ADHD and obesity are highly heritable complex conditions (Faraone et al., 2005, Chang et al., 2013, Locke et al., 2015) and have been found their respective familial aggregation, familial risk factors may predispose individuals to both conditions (Campbell and Eisenberg, 2007).

To date, however, there is a lack of evaluation on the familial co-aggregation of ADHD and overweight/obesity in a population-based family sample. The presence of familial risk factors common for both ADHD and overweight/obesity has not been rigorously tested.

Using data from the Swedish national and regional registers, we aimed to first estimate the association between ADHD and overweight/obesity among males, and then to examine whether ADHD and overweight/obesity share familial risk factors via demonstrating the familial co-aggregation of the two conditions in these males and their full siblings. Finally, we tested the hypothesis that the shared familial risk factors are not limited to those causing overweight/obesity through the mediation of ADHD.

## Methods

### *Data Sources and Study Population*

The Swedish Medical Birth Register provides information on approximately 98% of all births in Sweden since 1973 (Cnattingius et al., 1990). The Swedish Military Service Conscription Register contains information on physical and cognitive examination for Swedish males at approximately 18 years of age since 1968 (Gale et al., 2013). Males with foreign citizenship, severe medical condition, or intellectual disability were excused. By linking the two registers via unique personal identity numbers, we identified 472 735 males born in Sweden between 1973 and 1992, with information on body weight and height directly measured before they were conscripted for military service. We used these males as index persons to ascertain full sibships.

The Swedish Multi-Generation Register links those individuals born in Sweden since 1932 who were alive and living in Sweden on January 1, 1961 to their biological parents (Ekbom, 2011). Using this register, we further identified 523 237 full siblings (48.5% females) for the

index males. An index male and his full siblings shared both of their biological parents. The siblings of the index males were born in Sweden between 1973 and 2002 and living in Sweden during the years covered by this study. All individuals were followed up from their third birthday to December 31, 2009, when the youngest individuals were at age 7 and the oldest were at age 37. The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

*Definition of ADHD*

Individuals with ADHD were identified from the Swedish National Patient Register (SNPR), the Swedish Prescribed Drug Register (SPDR), and the Clinical Database for Child and Adolescent Psychiatry in Stockholm (Pastill). The SNPR contains discharge dates and diagnoses for psychiatric inpatient care since 1973 and outpatient visits to specialists since 2001 (Ludvigsson et al., 2011). Diagnoses in SNPR are coded according to *International Classification of Diseases, 8th revision (ICD-8)* between 1969 and 1986, *ICD-9* between 1987 and 1996, and *ICD-10* from 1997 onwards. The SPDR covers information on prescribing dates of all drugs coded by the anatomical therapeutic chemical classification system and dispensed to the entire population in Sweden since July 1, 2005 (Wettermark et al., 2007). Pastill includes data on discharge dates and diagnoses according to *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)* or *ICD-10* from Child and Adolescent Mental Health Services in Stockholm County since 2001 (Lundh et al., 2013). Individuals who, at any point before January 1st, 2010, received a diagnosis of hyperkinetic disorder (*ICD-9:* 314 or *ICD-10:* F90) according to the SNPR or the Pastill, or a diagnosis of ADHD (*DSM-IV:* 314) according to the Pastill, or a prescription of methylphenidate (N06BA04), amphetamine (N06BA01), dexamphetamine (N06BA02), or atomoxetine (N06BA09) according to the SPDR, were defined as ADHD cases.

*Definitions of overweight and obesity*

Data on weight and height directly measured by physician were retrieved from the Swedish Military Service Conscription Register (Batty et al., 2010). BMI was calculated as body weight in kilograms divided by height in meters squared, and categorized into normal weight (18.5≤BMI<25), overweight (25≤BMI<30), and obesity (BMI≥30) according to World Health Organization guidelines (World Health Organization., 2000). Individuals older than 21 years of age at conscription were excluded to diminish age-related variation in BMI. Individuals with BMI below 18.5 were also excluded to avoid analyzing a possible "U-shape" relationship between ADHD and BMI.

*Measurements of covariates*

In addition, family education and comorbid psychiatric conditions, including depression, anxiety, and substance use disorder, were involved as covariates. Family education was defined as the highest educational attainment of either parent. Information on family education was retrieved from the *Longitudinal Integration Database for Health Insurance and Labor Market* (Statistics Sweden, 2011) and categorized into elementary & upper secondary education (≤12 years), and higher education (≥13 years). Diagnoses of depression (*ICD-8:* 296.2, 298.0, 300.4; *ICD-9:* 296B, 300E; *ICD-10:* F32–F34), anxiety (*ICD-8:* 300 except 300.4; *ICD-9:* 300 except 300E; *ICD-10:* F40–F42, F44–F45, F48), and substance use disorder (*ICD-8:* 303–304; *ICD-9:* 303–305; *ICD-10:* F10–F19) were extracted from the SNPR and treated as binary variables (presence/absence).

*Statistical analysis*

Chi-square tests were used to assess whether there was significant difference in descriptive characteristics by BMI level in index males and by ADHD status in full siblings.

Analyses in index males

Logistic regression models were used to estimate birth year adjusted ORs and 95% confidence intervals (CIs), which measured the strength of the association between ADHD and overweight/obesity among index males. The models were further adjusted for family education and comorbid psychiatric conditions.

Analyses in index males and their full siblings

Logistic regression models were also used to assess the familial co-aggregation of ADHD and overweight/obesity, i.e., the association between overweight/obesity in index males and ADHD in their full siblings while adjusting for birth year of the index male and sex of the sibling. Familial co-aggregation of the two conditions, if present, can be jointly explained by (1) familial risk factors causing overweight/obesity through the mediation of ADHD, and (2) other familial risk factors shared by ADHD and overweight/obesity. When the models were further adjusted for ADHD status of the index male, a statistically significant positive association (OR>1) would indicate the presence of the second type of familial risk factors (Hudson et al., 2008). Detailed description about the rationale for the method based on a directed acyclic graph (DAG) (Figure S1) can be found in the online Supplement 1.

Sensitivity analyses

As a complementary evaluation of the familial co-aggregation, we further estimated the association between overweight/obesity in index persons and their full cousins. Full cousins were offspring of index persons' uncles or aunts. In total, we identified 2 138 440 cousins (48.6% females) for the index males. Significant associations would confirm the presence of familial risk factors shared by both conditions for two reasons. First, the total number of identified cousin pairs largely exceeded that of sibling pairs, giving higher statistical power to

capture the familial co-aggregation, though possibly weaker, with improved certainty. Second, compared to siblings, cousins were less affected by carryover effects (i.e., the presence of one condition in an individual affects the presence of the same or a different condition in his or her relatives) that could potentially complicate the interpretation of the familial co-aggregation results (D'Onofrio et al., 2013, Sjolander et al., 2016).

We examined whether the observed familial co-aggregation pertained to the entire population by conducting subgroup analyses stratified by family education level and by adding family education as an additional covariate. We repeated the main analyses first in sibling pairs with age difference less or equal to 5 years to minimize the impact of secular trends related to both ADHD and obesity, and then in sibling pairs where the index males were born before 1989 to not only reexamine the impact of secular trends but also limit the influence of missingness on BMI for index males due to the fact that the mandatory enlistment tests had been removed in 2007.

Robust standard errors were used to account for non-independence of family-clustered data. Significance level for all the tests was set at $p < .05$, 2 tailed. SAS software version 9.4 (SAS Institute Inc., Cary, NC) was used for data management and construction of analytic datasets. Stata software version 14(StataCorp., 2015) was used for statistical analyses.

## Results

*Description of the study population*

---- *Please insert Table 1 here* ----

Among 472 735 index males included in the study, 384 525 (81.34%) had normal weight, 68 906 (14.58%) had overweight, and 19 304 (4.08%) had obesity. The lifetime prevalence of

ADHD was 0.64% in index males and 0.87% in their full siblings. The average age difference between the index males and their full siblings was 4.54 (standard deviation=2.92) years. Additional descriptive characteristics of index males by BMI level and full siblings by ADHD status are shown in Table 1&2.

---- *Please insert Table 2 here* ----

*Association between ADHD and overweight/obesity in index males*

Among index males, ADHD was positively associated with overweight (OR=1.31, 95% CI=1.19–1.44) and obesity (OR=2.00, 95% CI=1.74–2.30) while adjusting for birth year. After additional adjustment for family education and comorbid psychiatric conditions, the associations remained significant for both overweight (OR=1.30, 95% CI=1.18 – 1.44) and obesity (OR=1.86, 95% CI=1.59–2.17).

*Familial co-aggregation of ADHD and overweight/obesity in full siblings*

---- *Please insert Table 3 here* ---

Sibling of index males with overweight/obesity were at significantly increased risk for ADHD compared to siblings of index males with normal weight (Overweight: OR=1.14, 95% CI=1.05–1.24; Obesity: OR=1.42, 95% CI=1.24–1.63; Table3). The ORs were adjusted for birth year of the index male and sex of the sibling. Analyses stratified by sex of the full sibling generated similar results (Table 3). After further adjustment for ADHD status of the index male, the associations remained significant (Overweight: OR=1.13, 95% CI=1.04–1.22; Obesity: OR=1.38, 95% CI=1.21–1.57; Table 3). These results indicate the presence of familial risk factors common for both ADHD and overweight/obesity.

*Sensitivity analyses*

---- *Please insert Table 4 here* ---

Familial co-aggregation of ADHD and overweight/obesity was also observed among index males and their full cousins (Table 4), with the results being similar for male and female cousins. Among sibling pairs, the co-aggregation of ADHD and obesity pertained across family education level, whereas the co-aggregation of ADHD and overweight was less robust, with the OR being non-significant in siblings from families of relatively lower education level (Table 4). Analyses restricted in sibling pairs with age difference less or equal to 5 years and in sibling pairs where the index males were born before 1989 gave significant ORs (Table 4). These results together suggest that the secular trends and the missingness on BMI of index males only exerted limited impact on the overall estimation of the familial co-aggregation between ADHD and overweight/obesity.

**Discussion**

In this population-based cohort study, we observed a significant association between ADHD and overweight/obesity among males while taking into account the influences of family education and comorbid psychiatric conditions (i.e., depression, anxiety, and substance use disorder). Furthermore, siblings of index males with overweight/obesity were at higher risk of ADHD compared to siblings of index males with normal weight. The observed familial co-aggregation was not fully explained by familial risk factors causing overweight/obesity through the medication of ADHD, and the results were also robust across several sensitivity analyses. The presence of other familial risk factors common for both conditions supports that ADHD and overweight/obesity overlap substantively in their etiological underpinnings.

Previous research on ADHD and overweight/obesity has predominantly focused on estimating the association between the two conditions (Cortese et al., 2015), with the underlying

mechanisms of the association being largely unknown. Familial risk factors shared by ADHD and overweight/obesity may explain the increased likelihood of the co-occurrence of the two conditions to the same individual as well as the co-aggregation of the two conditions within the same family. Previous literature has linked the common neurobiological dysfunctions of ADHD and obesity to reward deficiency due to changes in mesolimbic and mesocortical dopamine pathways (Campbell and Eisenberg, 2007). For example, decreased engagement of physical activity and prolonged television viewing have been observed in individuals with high BMI or ADHD (Eisenmann et al., 2008, Kim et al., 2011), which might be explained by poor cognitive control of physical activity caused by reward deficiency (Buckley et al., 2014). It is possible that reward deficiency might act as a common distal causal component leading to the development of ADHD and overweight/obesity via different biological pathways. In addition, mutations in the melanocortin 4 receptor (MC4R) gene and brain-derived neurotrophic factor (BDNF) gene variants have showed possible associations with both ADHD and obesity, even though the evidence is inconsistent (Albayrak et al., 2013, Shinawi et al., 2011, Friedel et al., 2005). A recent meta-analysis based on more than 300,000 individuals identified 97 genome-wide significance loci accounting for up to 2.7% of BMI variation (Locke et al., 2015). Similar level of progress in molecular genetic research on ADHD has not yet been achieved (Neale et al., 2010). By showing the evidence for the existence of shared etiological underpinnings between the two conditions, the present study may serve as an important first step leading towards a better understanding of the etiology of ADHD and, ultimately, the exploration of novel effective pathophysiology-based treatments for both ADHD and overweight/obesity.

The strengths of the present study include the use of a population-based sample and the Multi-Generation Register, which enabled unambiguous identification of the siblings and cousins of the index males. Prospectively collected and directly measured data on body weight and

height precluded recall bias. The ascertainment of ADHD cases via both clinical diagnosis and prescribed medication tend to capture individuals with severe forms of the disorder. This could to a large extent reduce the chance of false positives, even though false negatives could not be avoided. Finally, using DAG to visualize the assumed underlying mechanisms of the research question substantially facilitated the analytic process of identifying biases and making statistical adjustments.

The study could not avoid certain limitations. First, the prevalence of ADHD in the present study was lower compared to previously reported by the meta-analysis (Cortese et al., 2015). The discrepancy might be attributed to (1) the suboptimal coverage of the Swedish registers for outpatient visits before 2001 and (2) failure or delay in seeking medical care by individuals under study. The resulting misclassification of ADHD cases might dilute the estimated associations. Second, the lack of data on BMI for females did not allow further exploration of the familial co-aggregation of ADHD and overweight/obesity among index females and their relatives. Such familial co-aggregation has been suggested in one sibling-comparison study showing that familial factors shared by mothers and their offspring at least in part explain the overrepresentation of ADHD among offspring born to mothers with pre-pregnancy overweight/obesity (Chen et al., 2014). Third, we did not make distinction between medicated and unmedicated index males. Stimulant medications may influence BMI of children and adolescents due to their documented side effects, such as reduced appetite and small delays in growth (Faraone et al., 2008). Although future work should address issues concerning the effects of medications on the associations under study, they are unlikely to have accounted for our significant findings.

In conclusion, ADHD and overweight/obesity share familial risk factors, which are not limited to those causing overweight/obesity through the mediation of ADHD, indicating that

ADHD and overweight/obesity might be different manifestations of substantively overlapped pathophysiology. Future research aiming at identifying family-wide environmental risk factors as well as common pleiotropic genetic variants contributing to ADHD and overweight/obesity is warranted and may reveal valuable insights into novel treatment approaches for both conditions.

**Key points**

- Full siblings of index males with overweight/obesity are at higher risk of ADHD compared to full siblings of index males with normal weight.
- The familial co-aggregation of ADHD and overweight/obesity is at least in part driven by shared familial risk factors between the two conditions.
- Future research aiming at identifying family-wide environmental risk as well as common pleiotropic genetic variants contributing to both ADHD and overweight/obesity is warranted and may aid in exploring effective pathophysiology-based treatments for both conditions.

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## References


Albayrak, O., Putter, C., Volckmar, A. L., Cichon, S., Hoffmann, P., Nothen, M. M., Jockel, K. H., Schreiber, S., Wichmann, H. E., Faraone, S. V., Neale, B. M., Herpertz-Dahlmann, B., Lehmkuhl, G., Sinzig, J., Renner, T. J., Romanos, M., Warnke, A., Lesch, K. P., Reif, A., Schimmelmann, B. G., Scherag, A., Hebebrand, J. & Hinney, A. (2013). Common obesity risk alleles in childhood attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet,* 162B**,** 295-305.

Batty, G. D., Whitley, E., Kivimaki, M., Tynelius, P. & Rasmussen, F. (2010). Body mass index and attempted suicide: Cohort study of 1,133,019 Swedish men. *Am J Epidemiol,* 172**,** 890-899.

Buckley, J., Cohen, J. D., Kramer, A. F., McAuley, E. & Mullen, S. P. (2014). Cognitive control in the self-regulation of physical activity and sedentary behavior. *Front Hum Neurosci,* 8**,** 747.

Campbell, B. C. & Eisenberg, D. (2007). Obesity, attention deficit-hyperactivity disorder and the dopaminergic reward system. *Coll Antropol,* 31**,** 33-38.

Chang, Z., Lichtenstein, P., Asherson, P. J. & Larsson, H. (2013). Developmental twin study of attention problems: high heritabilities throughout development. *JAMA Psychiatry,* 70**,** 311-318.

Chen, Q., Sjolander, A., Langstrom, N., Rodriguez, A., Serlachius, E., D'Onofrio, B. M., Lichtenstein, P. & Larsson, H. (2014). Maternal pre-pregnancy body mass index and offspring attention deficit hyperactivity disorder: a population-based cohort study using a sibling-comparison design. *Int J Epidemiol,* 43**,** 83-90.

Chorozoglou, M., Smith, E., Koerting, J., Thompson, M. J., Sayal, K. & Sonuga-Barke, E. J. (2015). Preschool hyperactivity is associated with long-term economic burden: evidence from a longitudinal health economic analysis of costs incurred across childhood, adolescence and young adulthood. *J Child Psychol Psychiatry,* 56**,** 966-975.

Cnattingius, S., Ericson, A., Gunnarskog, J. & Kallen, B. (1990). A quality study of a medical birth registry. *Scand J Soc Med,* 18**,** 143-148.

Cortese, S. & Castellanos, F. X. (2014). The relationship between ADHD and obesity: implications for therapy. *Expert Rev Neurother,* 14**,** 473-479.

Cortese, S., Moreira-Maia, C. R., St Fleur, D., Morcillo-Penalver, C., Rohde, L. A. & Faraone, S. V. (2015). Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. *Am J Psychiatry***,** appiajp201515020266.

D'Onofrio, B. M., Lahey, B. B., Turkheimer, E. & Lichtenstein, P. (2013). Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *Am J Public Health,* 103 Suppl 1**,** S46-55.

Eisenmann, J. C., Bartee, R. T., Smith, D. T., Welk, G. J. & Fu, Q. (2008). Combined influence of physical activity and television viewing on the risk of overweight in US youth. *Int J Obes (Lond),* 32**,** 613-618.

Ekbom, A. (2011). The Swedish Multi-generation Register. *Methods Mol Biol,* 675**,** 215-220.

Faraone, S. V., Biederman, J., Morley, C. P. & Spencer, T. J. (2008). Effect of stimulants on height and weight: a review of the literature. *J Am Acad Child Adolesc Psychiatry,* 47**,** 994-1009.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A. & Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry,* 57**,** 1313-1323.

Fayyad, J., De Graaf, R., Kessler, R., Alonso, J., Angermeyer, M., Demyttenaere, K., De Girolamo, G., Haro, J. M., Karam, E. G., Lara, C., Lepine, J. P., Ormel, J., Posada-Villa, J., Zaslavsky, A. M. & Jin, R. (2007). Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *Br J Psychiatry,* 190**,** 402-409.

Friedel, S., Horro, F. F., Wermter, A. K., Geller, F., Dempfle, A., Reichwald, K., Smidt, J., Bronner, G., Konrad, K., Herpertz-Dahlmann, B., Warnke, A., Hemminger, U., Linder, M., Kiefl, H., Goldschmidt, H. P., Siegfried, W., Remschmidt, H., Hinney, A. & Hebebrand, J. (2005).

Mutation screen of the brain derived neurotrophic factor gene (BDNF): identification of several genetic variants and association studies in patients with obesity, eating disorders, and attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet,* 132b**,** 96-99.

Gale, C. R., Batty, G. D., McIntosh, A. M., Porteous, D. J., Deary, I. J. & Rasmussen, F. (2013). Is bipolar disorder more common in highly intelligent people? A cohort study of a million men. *Mol Psychiatry,* 18**,** 190-194.

Gariepy, G., Nitka, D. & Schmitz, N. (2010). The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. *Int J Obes (Lond),* 34**,** 407-419.

Hudson, J. I., Javaras, K. N., Laird, N. M., VanderWeele, T. J., Pope, H. G., Jr. & Hernan, M. A. (2008). A structural approach to the familial coaggregation of disorders. *Epidemiology,* 19**,** 431-439.

Kim, J., Mutyala, B., Agiovlasitis, S. & Fernhall, B. (2011). Health behaviors and obesity among US children with attention deficit hyperactivity disorder by gender and medication use. *Prev Med,* 52**,** 218-222.

Locke, A. E., Kahali, B., Berndt, S. I., Justice, A. E., Pers, T. H., Day, F. R., Powell, C., Vedantam, S., Buchkovich, M. L., Yang, J., Croteau-Chonka, D. C., Esko, T., Fall, T., Ferreira, T., Gustafsson, S., Kutalik, Z., Luan, J., Magi, R., Randall, J. C., Winkler, T. W., Wood, A. R., Workalemahu, T., Faul, J. D., Smith, J. A., Hua Zhao, J., Zhao, W., Chen, J., Fehrmann, R., Hedman, A. K., Karjalainen, J., Schmidt, E. M., Absher, D., Amin, N., Anderson, D., Beekman, M., Bolton, J. L., Bragg-Gresham, J. L., Buyske, S., Demirkan, A., Deng, G., Ehret, G. B., Feenstra, B., Feitosa, M. F., Fischer, K., Goel, A., Gong, J., Jackson, A. U., Kanoni, S., Kleber, M. E., Kristiansson, K., Lim, U., Lotay, V., Mangino, M., Mateo Leach, I., Medina-Gomez, C., Medland, S. E., Nalls, M. A., Palmer, C. D., Pasko, D., Pechlivanis, S., Peters, M. J., Prokopenko, I., Shungin, D., Stancakova, A., Strawbridge, R. J., Ju Sung, Y., Tanaka, T., Teumer, A., Trompet, S., van der Laan, S. W., van Setten, J., Van Vliet-Ostaptchouk, J. V., Wang, Z., Yengo, L., Zhang, W., Isaacs, A., Albrecht, E., Arnlov, J., Arscott, G. M., Attwood, A. P., Bandinelli, S., Barrett, A., Bas, I. N., Bellis, C., Bennett, A. J., Berne, C., Blagieva, R., Bluher, M., Bohringer, S., Bonnycastle, L. L., Bottcher, Y., Boyd, H. A., Bruinenberg, M., Caspersen, I. H., Ida Chen, Y. D., Clarke, R., Daw, E. W., de Craen, A. J., Delgado, G., Dimitriou, M., Doney, A. S., Eklund, N., Estrada, K., Eury, E., Folkersen, L., Fraser, R. M., Garcia, M. E., Geller, F., Giedraitis, V., Gigante, B., Go, A. S., Golay, A., Goodall, A. H., Gordon, S. D., Gorski, M., Grabe, H. J., Grallert, H., Grammer, T. B., Grassler, J., Gronberg, H., Groves, C. J., Gusto, G., Haessler, J., Hall, P., Haller, T., Hallmans, G., Hartman, C. A., Hassinen, M., Hayward, C., Heard-Costa, N. L., Helmer, Q., Hengstenberg, C., Holmen, O., Hottenga, J. J., James, A. L., Jeff, J. M., Johansson, A., Jolley, J., Juliusdottir, T., Kinnunen, L., Koenig, W., Koskenvuo, M., Kratzer, W., Laitinen, J., Lamina, C., Leander, K., Lee, N. R., Lichtner, P., Lind, L., Lindstrom, J., Sin Lo, K., Lobbens, S., Lorbeer, R., Lu, Y., Mach, F., Magnusson, P. K., Mahajan, A., McArdle, W. L., McLachlan, S., Menni, C., Merger, S., Mihailov, E., Milani, L., Moayyeri, A., Monda, K. L., Morken, M. A., Mulas, A., Muller, G., Muller-Nurasyid, M., Musk, A. W., Nagaraja, R., Nothen, M. M., Nolte, I. M., Pilz, S., Rayner, N. W., Renstrom, F., Rettig, R., Ried, J. S., Ripke, S., Robertson, N. R., Rose, L. M., Sanna, S., Scharnagl, H., Scholtens, S., Schumacher, F. R., Scott, W. R., Seufferlein, T., Shi, J., Vernon Smith, A., Smolonska, J., Stanton, A. V., Steinthorsdottir, V., Stirrups, K., Stringham, H. M., Sundstrom, J., Swertz, M. A., Swift, A. J., Syvanen, A. C., Tan, S. T., Tayo, B. O., Thorand, B., Thorleifsson, G., Tyrer, J. P., Uh, H. W., Vandenput, L., Verhulst, F. C., Vermeulen, S. H., Verweij, N., Vonk, J. M., Waite, L. L., Warren, H. R., Waterworth, D., Weedon, M. N., Wilkens, L. R., Willenborg, C., Wilsgaard, T., Wojczynski, M. K., Wong, A., Wright, A. F., Zhang, Q., Brennan, E. P., Choi, M., Dastani, Z., Drong, A. W., Eriksson, P., Franco-Cereceda, A., Gadin, J. R., Gharavi, A. G., Goddard, M. E., Handsaker, R. E., Huang, J., Karpe, F., Kathiresan, S., Keildson, S., Kiryluk, K., Kubo, M., Lee, J. Y., Liang, L., Lifton, R. P., Ma, B., McCarroll, S. A., McKnight, A. J., Min, J. L., Moffatt, M. F., Montgomery, G. W., Murabito, J. M., Nicholson, G., Nyholt, D. R., Okada, Y., Perry, J. R., Dorajoo, R., Reinmaa, E., Salem, R. M., Sandholm, N., Scott, R. A., Stolk, L., Takahashi, A., Van't Hooft, F. M., Vinkhuyzen, A. A., Westra, H. J., Zheng,

W., Zondervan, K. T., Heath, A. C., Arveiler, D., Bakker, S. J., Beilby, J., Bergman, R. N., Blangero, J., Bovet, P., Campbell, H., Caulfield, M. J., Cesana, G., Chakravarti, A., Chasman, D. I., Chines, P. S., Collins, F. S., Crawford, D. C., Cupples, L. A., Cusi, D., Danesh, J., de Faire, U., den Ruijter, H. M., Dominiczak, A. F., Erbel, R., Erdmann, J., Eriksson, J. G., Farrall, M., Felix, S. B., Ferrannini, E., Ferrieres, J., Ford, I., Forouhi, N. G., Forrester, T., Franco, O. H., Gansevoort, R. T., Gejman, P. V., Gieger, C., Gottesman, O., Gudnason, V., Gyllensten, U., Hall, A. S., Harris, T. B., Hattersley, A. T., Hicks, A. A., Hindorff, L. A., Hingorani, A. D., Hofman, A., Homuth, G., Hovingh, G. K., Humphries, S. E., Hunt, S. C., Hypponen, E., Illig, T., Jacobs, K. B., Jarvelin, M. R., Jockel, K. H., Johansen, B., Jousilahti, P., Jukema, J. W., Jula, A. M., Kaprio, J., Kastelein, J. J., Keinanen-Kiukaanniemi, S. M., Kiemeney, L. A., Knekt, P., Kooner, J. S., Kooperberg, C., Kovacs, P., Kraja, A. T., Kumari, M., Kuusisto, J., Lakka, T. A., Langenberg, C., Le Marchand, L., Lehtimaki, T., Lyssenko, V., Mannisto, S., Marette, A., Matise, T. C., McKenzie, C. A., McKnight, B., Moll, F. L., Morris, A. D., Morris, A. P., Murray, J. C., Nelis, M., Ohlsson, C., Oldehinkel, A. J., Ong, K. K., Madden, P. A., Pasterkamp, G., Peden, J. F., Peters, A., Postma, D. S., Pramstaller, P. P., Price, J. F., Qi, L., Raitakari, O. T., Rankinen, T., Rao, D. C., Rice, T. K., Ridker, P. M., Rioux, J. D., Ritchie, M. D., Rudan, I., Salomaa, V., Samani, N. J., Saramies, J., Sarzynski, M. A., Schunkert, H., Schwarz, P. E., Sever, P., Shuldiner, A. R., Sinisalo, J., Stolk, R. P., Strauch, K., Tonjes, A., Tregouet, D. A., Tremblay, A., Tremoli, E., Virtamo, J., Vohl, M. C., Volker, U., Waeber, G., Willemsen, G., Witteman, J. C., Zillikens, M. C., Adair, L. S., Amouyel, P., Asselbergs, F. W., Assimes, T. L., Bochud, M., Boehm, B. O., Boerwinkle, E., Bornstein, S. R., Bottinger, E. P., Bouchard, C., Cauchi, S., Chambers, J. C., Chanock, S. J., Cooper, R. S., de Bakker, P. I., Dedoussis, G., Ferrucci, L., Franks, P. W., Froguel, P., Groop, L. C., Haiman, C. A., Hamsten, A., Hui, J., Hunter, D. J., Hveem, K., Kaplan, R. C., Kivimaki, M., Kuh, D., Laakso, M., Liu, Y., Martin, N. G., Marz, W., Melbye, M., Metspalu, A., Moebus, S., Munroe, P. B., Njolstad, I., Oostra, B. A., Palmer, C. N., Pedersen, N. L., Perola, M., Perusse, L., Peters, U., Power, C., Quertermous, T., Rauramaa, R., Rivadeneira, F., Saaristo, T. E., Saleheen, D., Sattar, N., Schadt, E. E., Schlessinger, D., Slagboom, P. E., Snieder, H., Spector, T. D., Thorsteinsdottir, U., Stumvoll, M., Tuomilehto, J., Uitterlinden, A. G., Uusitupa, M., van der Harst, P., Walker, M., Wallaschofski, H., Wareham, N. J., Watkins, H., Weir, D. R., Wichmann, H. E., Wilson, J. F., Zanen, P., Borecki, I. B., Deloukas, P., Fox, C. S., Heid, I. M., O'Connell, J. R., Strachan, D. P., Stefansson, K., van Duijn, C. M., Abecasis, G. R., Franke, L., Frayling, T. M., McCarthy, M. I., Visscher, P. M., Scherag, A., Willer, C. J., Boehnke, M., Mohlke, K. L., Lindgren, C. M., Beckmann, J. S., Barroso, I., North, K. E., Ingelsson, E., Hirschhorn, J. N., Loos, R. J. & Speliotes, E. K. (2015). Genetic studies of body mass index yield new insights for obesity biology. *Nature,* 518**,** 197-206.

Ludvigsson, J. F., Andersson, E., Ekbom, A., Feychting, M., Kim, J. L., Reuterwall, C., Heurgren, M. & Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health,* 11**,** 450.

Lundh, A., Forsman, M., Serlachius, E., Lichtenstein, P. & Landen, M. (2013). Outcomes of child psychiatric treatment. *Acta Psychiatr Scand,* 128**,** 34-44.

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W. & Zitman, F. G. (2010). Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry,* 67**,** 220-229.

Muller-Riemenschneider, F., Reinhold, T., Berghofer, A. & Willich, S. N. (2008). Health-economic burden of obesity in Europe. *Eur J Epidemiol,* 23**,** 499-509.

Neale, B. M., Medland, S. E., Ripke, S., Asherson, P., Franke, B., Lesch, K. P., Faraone, S. V., Nguyen, T. T., Schafer, H., Holmans, P., Daly, M., Steinhausen, H. C., Freitag, C., Reif, A., Renner, T. J., Romanos, M., Romanos, J., Walitza, S., Warnke, A., Meyer, J., Palmason, H., Buitelaar, J., Vasquez, A. A., Lambregts-Rommelse, N., Gill, M., Anney, R. J., Langely, K., O'Donovan, M., Williams, N., Owen, M., Thapar, A., Kent, L., Sergeant, J., Roeyers, H., Mick, E., Biederman, J., Doyle, A., Smalley, S., Loo, S., Hakonarson, H., Elia, J., Todorov, A., Miranda, A., Mulas, F., Ebstein, R. P., Rothenberger, A., Banaschewski, T., Oades, R. D., Sonuga-Barke, E., McGough,

J., Nisenbaum, L., Middleton, F., Hu, X. & Nelson, S. (2010). Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry,* 49**,** 884-897.

Neovius, K., Johansson, K., Kark, M., Tynelius, P. & Rasmussen, F. (2013). Trends in self-reported BMI and prevalence of obesity 2002-10 in Stockholm County, Sweden. *Eur J Public Health,* 23**,** 312-315.

Neovius, M., Janson, A. & Rossner, S. (2006). Prevalence of obesity in Sweden. *Obes Rev,* 7**,** 1-3.

Ogden, C. L., Carroll, M. D., Kit, B. K. & Flegal, K. M. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA,* 311**,** 806-814.

Polanczyk, G. V., Salum, G. A., Sugaya, L. S., Caye, A. & Rohde, L. A. (2015). Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry,* 56**,** 345-365.

Shinawi, M., Sahoo, T., Maranda, B., Skinner, S. A., Skinner, C., Chinault, C., Zascavage, R., Peters, S. U., Patel, A., Stevenson, R. E. & Beaudet, A. L. (2011). 11p14.1 microdeletions associated with ADHD, autism, developmental delay, and obesity. *Am J Med Genet A,* 155a**,** 1272-1280.

Simon, V., Czobor, P., Balint, S., Meszaros, A. & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry,* 194**,** 204-211.

Sjolander, A., Frisell, T., Kuja-Halkola, R., Oberg, S. & Zetterqvist, J. (2016). Carryover Effects in Sibling Comparison Designs. *Epidemiology,* 27**,** 852-858.

StataCorp. (2015). Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.

Statistics Sweden (2011). Longitudinell integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier (LISA) 1990-2009. Sweden: Statistics Sweden.

Thomas, R., Sanders, S., Doust, J., Beller, E. & Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics,* 135**,** e994-1001.

Wang, Y. & Beydoun, M. A. (2007). The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev,* 29**,** 6-28.

Wettermark, B., Hammar, N., Fored, C. M., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundstrom, A., Westerholm, B. & Rosen, M. (2007). The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf,* 16**,** 726-735.

World Health Organization. (2000). *Obesity : preventing and managing the global epidemic : report of a WHO consultation,* Geneva: World Health Organization.

**Table 1 Descriptive characteristics of index males by BMI level**

| Variable | Normal weight, n (%) | Overweight, n (%) | Obesity, n (%) | P Value |
|---|---|---|---|---|
| Total, n (%) | 384 525 (81.34) | 68 906 (14.58) | 19 304 (4.08) | |
| ADHD | 2 269 (0.59) | 526 (0.76) | 222 (1.15) | < .001 |
| Family education | | | | |
| Elementary & upper secondary (≤12 years) | 204 677 (53.23) | 41 529 (60.27) | 13 283 (68.81) | Reference |
| Higher (≥13 years) | 179 749 (46.75) | 27 359 (39.70) | 6 019 (31.18) | < .001 |
| Missing | 99 (0.03) | 18 (0.03) | 2 (0.01) | |
| Comorbidity | | | | |
| Depression | 7 762 (2.02) | 1 400 (2.03) | 510 (2.64) | < .001 |
| Anxiety | 8 557 (2.23) | 1 430 (2.08) | 501 (2.60) | < .001 |
| Substance use disorder | 12 132 (3.16) | 2 230 (3.24) | 655 (3.39) | .115 |

**Table 2 Descriptive characteristics of index males and their full siblings by ADHD status**

| Variable | Without ADHD, n (%) | With ADHD, n (%) | P Value |
|---|---|---|---|
| Index males (n=472 735) | | | |
| Total, n (%) | 469 718 (99.36) | 3017 (0.64) | |
| BMI of index male | | | |
| Normal weight | 382 256 (81.38) | 2 269 (75.21) | Reference |
| Overweight | 68 380 (14.56) | 526 (17.43) | < .001 |
| Obesity | 19 082 (4.06) | 222 (7.36) | < .001 |
| Family education | | | |
| Elementary & upper secondary (≤12 years) | 257 652 (54.85) | 1 837 (60.89) | Reference |
| Higher (≥13 years) | 211 954 (45.12) | 1 173 (38.88) | < .001 |
| Missing | 112 (0.02) | 7 (0.23) | |
| Comorbidity | | | |
| Depression | 8 788 (1.87) | 884 (29.30) | < .001 |
| Anxiety | 9 518 (2.03) | 970 (32.15) | < .001 |
| Substance use disorder | 13 957 (2.97) | 1 060 (35.13) | < .001 |
| Full siblings of index males (n=523 237) | | | |
| Total, n (%) | 518 675 (99.13) | 4 562 (0.87) | |
| Sex, n (%) | | | |
| Male | 266 599 (98.90) | 2 975 (1.10) | Reference |
| Female | 252 076 (99.37) | 1 587 (0.63) | < .001 |
| BMI of index male | | | |
| Normal weight | 422 437 (81.45) | 3 552 (77.86) | Reference |
| Overweight | 75 312 (14.52) | 747 (16.37) | < .001 |
| Obesity | 20 926 (4.03) | 263 (5.77) | < .001 |
| Family education | | | |
| Elementary & upper secondary (≤12 years) | 272 292 (52.50) | 2 718 (59.58) | Reference |
| Higher (≥13 years) | 246 300 (47.49) | 1 841 (40.36) | < .001 |
| Missing | 83 (0.02) | 3 (0.07) | |
| Comorbidity | | | |
| Depression | 15 062 (2.90) | 1 174 (25.73) | < .001 |
| Anxiety | 15 829 (3.05) | 1 265 (27.73) | < .001 |
| Substance use disorder | 13 544 (2.61) | 1 058 (23.19) | < .001 |

**Table 3 Associations between overweight/obesity in index males and ADHD in their full siblings**

| | Adjusting for ADHD status of the index male | | | |
|---|---|---|---|---|
| | No | | Yes | |
| **BMI level of index males** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| All full siblings (n=523 237 pairs) | | | | |
| Normal weight | Reference | | Reference | |
| Overweight | 1.14 (1.05–1.24) | .002 | 1.13 (1.04–1.22) | .005 |
| Obesity | 1.42 (1.24–1.63) | < .001 | 1.38 (1.21–1.57) | < .001 |
| Female full siblings (n=253 663 pairs) | | | | |
| Normal weight | Reference | | Reference | |
| Overweight | 1.19 (1.03–1.36) | .015 | 1.17 (1.02–1.34) | .021 |
| Obesity | 1.30 (1.03–1.63) | .027 | 1.26 (1.00–1.59) | .048 |
| Male full siblings (n=269 574 pairs) | | | | |
| Normal weight | Reference | | Reference | |
| Overweight | 1.12 (1.01–1.23) | .034 | 1.10 (0.99–1.22) | .066 |
| Obesity | 1.49 (1.27–1.75) | < .001 | 1.44 (1.23–1.69) | < .001 |

ORs were also adjusted for birth year of the index male and sex of the sibling (analyses in all full siblings)

**Table 4 Influences of cousinship, family education level, and secular trends on familial co-aggregation of ADHD and overweight/obesity**

| | Overweight | | Obesity | |
|---|---|---|---|---|
| **Sensitivity analysis** | **OR (95% CI)** | **P Value** | **OR (95% CI)** | **P Value** |
| Familial co-aggregation of ADHD and overweight/obesity in full cousins | | | | |
| All full cousins (n=2 138 440 cousin pairs) | 1.11 (1.07–1.15) | < .001 | 1.29 (1.22–1.37) | < .001 |
| Female full cousins (n=1 038 696 cousin pairs) | 1.10 (1.04–1.17) | .002 | 1.28 (1.17–1.41) | < .001 |
| Male full cousins (n=1 099 744 cousin pairs) | 1.11 (1.07–1.16) | < .001 | 1.30 (1.21–1.39) | < .001 |
| Analyses stratified by family education level | | | | |
| Elementary & upper secondary (n=275 010 sibling pairs) | 1.00 (0.90–1.12) | .965 | 1.21 (1.03–1.43) | .019 |
| Higher (n=248 141 sibling pairs) | 1.25 (1.10–1.43) | .001 | 1.50 (1.19–1.89) | .001 |
| Analyses adjusted for family education (n=523 151 sibling pairs) | 1.09 (1.01–1.19) | .035 | 1.30 (1.14–1.49) | < .001 |
| Sibling pairs with age difference ≤ 5 years (n=376 421 sibling pairs) | 1.11(1.00–1.22) | .044 | 1.33 (1.14–1.56) | < .001 |
| Index males born before 1989 (n=472 993 sibling pairs) | 1.13 (1.03–1.24) | .008 | 1.42 (1.23–1.64) | < .001 |

ORs were also adjusted for birth year and ADHD status of the index male as well as sex of the relative; Overweight and obesity were compared with normal weight; Elementary & upper secondary education: education ≤ 12 years; Higher education: education ≥ 13 years.