Schizophrenia Research 206 (2019) 313–317

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Body mass index trajectories in childhood and adolescence - Risk for non-affective psychosis

Elina Sormunen [a], Maiju M. Saarinen [b], Raimo K.R. Salokangas [a], Nina Hutri-Kähönen [c], Jorma S.A. Viikari [d], Olli T. Raitakari [b,e], Jarmo Hietala [a,f,*]

[a] Department of Psychiatry, University of Turku, Turku, Finland
[b] Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
[c] Department of Pediatrics, University of Tampere and Tampere University Hospital, Tampere, Finland
[d] Department of Medicine, University of Turku and Division of Medicine, Turku University Hospital, Turku, Finland
[e] Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland
[f] General Hospital Psychiatry Unit, Turku University Hospital, Turku, Finland and Turku Psychiatry, Turku, Finland

ARTICLE INFO

Article history:
Received 7 June 2018
Received in revised form 14 October 2018
Accepted 23 October 2018
Available online 26 October 2018

Keywords:
Risk for schizophrenia
Risk for psychiatric disorder
Underweight
Overweight
Cohort study

ABSTRACT

Background: Underweight in early adulthood increases risk for schizophrenia, but the effect of early childhood underweight on psychosis risk is not well known.
Methods: We studied whether underweight or overweight in childhood and adolescence increases risk for non-affective psychosis or other psychiatric disorders in a population-based cohort study 'Cardiovascular Risk in Young Finns'. Body mass index (BMI) trajectories were recorded in the years 1980, 1983 and 1986 (in 3–18 years of age), before the first hospitalization due to a psychiatric disorder. BMI was categorized as underweight, normal weight or overweight, using the BMI classification for children and adolescents. We formed DSM-IV based diagnostic groups of non-affective psychosis (n = 69, including a schizophrenia subgroup, n = 41) and affective disorders (i.e. mood and anxiety disorders, n = 112) based on the Care Register for Health Care. Groups were compared with subjects with no psychiatric diagnoses (n = 3310). Sex, age, low birthweight and mother's mental disorders were included in the analyses.
Results: Underweight, but not overweight, independently predicted later development of non-affective psychosis. The risk of psychosis was over two-fold (relative risk (RR) [95% CI] 2.31 [1.2–4.4]) and of schizophrenia nearly 2.5-fold (RR 2.44 [1.03–5.8]) after underweight in childhood/adolescence. Underweight or overweight in childhood and adolescence was not associated with mood or anxiety disorders.
Conclusions: These results support the hypothesis of non-affective psychosis as a neurodevelopmental disorder with somatic manifestations throughout childhood and adolescence.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

Recent studies have provided increasing amount of evidence of schizophrenia as a neurodevelopmental disorder (Insel, 2010). One aspect is the finding that suboptimal growth in childhood and adolescence is associated with the risk of psychosis later in life. Low birthweight is a risk factor for schizophrenia, as shown in a large cohort study conducted in Sweden and Denmark (Abel et al., 2010). Very few studies have been made concerning deviation from normal weight in childhood in this group. In 1994 Jones et al. did not find a significant difference in height or weight between 7 and 11 years old children with future schizophrenia and controls (Jones et al., 1994). Two separate studies have shown the association between childhood underweight and future schizophrenia or psychosis. Wahlbeck et al. have shown that children and adolescents, who later developed psychosis, had lower birthweight, were shorter at birth and, at the age of 7 to 15 years, thinner than comparison subjects (Wahlbeck et al., 2001). Similar results were shown by Sørensen et al.; low birthweight and low BMI at the age of 7 to 13 years were associated with the risk of schizophrenia (Sørensen et al., 2016). Furthermore, low BMI in adolescence or early adulthood is well known to predict later schizophrenia (Gunnell et al., 2005; Sørensen et al., 2006; Weiser et al., 2004; Zammit et al., 2007). Most of these studies, however, included only men (Sørensen et al., 2006; Weiser et al., 2004; Zammit et al., 2007) and some results, that have been inconsistent with previously mentioned studies, have also been published. A Swedish cohort study with 334,577 males did not find a significant difference in BMI at the time of military conscription (mean age 18) between controls and patients with future schizophrenia

* Corresponding author at: Department of Psychiatry, University of Turku, Kunnallissairaalantie 20, Building 9, 20700 Turku, Finland.
E-mail address: jahi@utu.fi (J. Hietala).

https://doi.org/10.1016/j.schres.2018.10.025
0920-9964/© 2018 Elsevier B.V. All rights reserved.

(Gunnell et al., 2003). Further, Wyatt et al. studied US armed forces personnel and found no association between BMI and later development of schizophrenia, bipolar disorder or major depressive disorder (Wyatt et al., 2003).

Based on epidemiologic and genetic research, there is increasing evidence that mental disorders have partially common pathophysiological factors. The risk of schizophrenia is associated not only with family history of schizophrenia, but with family history of wide range of other mental disorders as well (Mortensen et al., 2010). Genetic studies confirm this impression: a significant part of genetic susceptibility is common in schizophrenia, bipolar disorder and major depression (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). We, therefore, assumed that deviation from normal weight could also affect the risk of mental disorders other than psychosis. Some studies have shown that overweight or obesity in childhood, adolescence or both may predict depression (Anderson et al., 2007; Herva et al., 2006; Sanderson et al., 2011), but we are not aware of any studies concerning underweight in childhood and the risk of mental disorders other than psychosis.

Our aim was to study whether deviation from normal weight, i.e. underweight or overweight, in early childhood and adolescence predicts later development of non-affective psychosis, by utilizing a population-based cohort study and hospital discharge register. In addition, we explored whether the mechanism is specific to psychosis or whether the BMI trajectories associate with an altered risk for mood and anxiety disorders as well.

2. Methods

2.1. Study sample

The Cardiovascular Risk in Young Finns Study (YFS) is an epidemiologic, population based, follow-up study of the risk factors for coronary heart disease (Raitakari et al., 2008). The subjects of YFS were randomly selected from the population register of five Finnish university cities (Helsinki, Kuopio, Oulu, Tampere and Turku) and their rural surroundings. A total of 3596 children and adolescents from six age groups between 3 and 18 years participated in the first cross-sectional survey in 1980. The cohort was re-examined in three-year intervals until 1986. In the present study, measurements from the first three follow-ups of 1980, 1983 and 1986 were included, up to the participants' age of 18 years. The next follow-up for all participants was in 2001, when even the youngest participants were 24 years old and therefore excluded.

Psychiatric diagnoses of the participants were acquired from the Care Register for Health Care (HILMO), previously called the Hospital Discharge Register. This register was established in 1969 and it covers all hospitals in Finland. It is maintained by the National Institute for Health and Welfare. Diagnoses up to the year 2014 were included, covering follow-up to age 37–52 years for all participants. ICD-diagnoses were converted to DSM-IV diagnoses as described previously by Sormunen et al. (Sormunen et al., 2017). Cut-off age for analysis of the premorbid or prodromal phase of psychosis in our study was 18 years.

Participants who were diagnosed with any psychiatric disorder during 1980–1986 were excluded from the analysis; one participant from non-affective psychosis group and three participants from affective disorders group. Four participants, one from non-affective psychosis group and three from controls, had no BMI measurements during years 1980–1986. Therefore, from a total of 3596 participants, 3588 participants were available for analysis. Full data from all three study visits (1980–1986) were available from 49% of the 3588 participants. 24% of participants had two visits and 27% just one visit.

In this cohort, 71 (2.0%) of total 3596 participants were later hospitalized for non-affective psychosis. From a total of 71 participants who later developed non-affective psychosis, 69 were available for analysis, 41 (59%) men and 28 (41%) women. In the group of future non-affective psychosis, 41 (59%) of the subjects had schizophrenia, schizophreniform disorder or schizoaffective disorder (DSM-IV 295), resulting in a 1.1% prevalence in this population. Delusional disorder (DSM-IV 297) was diagnosed in 6 (9%) participants and brief psychotic disorder or psychotic disorder NOS (DSM-IV 298) in 22 (32%) participants. The prevalences for other hospital-related psychiatric diagnostic groups were 3.1% (n = 112) for affective disorders (mood and anxiety disorders, DSM-IV 296, 300, 311), 1.2% (n = 44) for personality disorders (DSM-IV 301) and 1.5% (n = 53) for substance-related disorders (DSM-IV 291, 303, 292, 304, 305). Controls are subjects who did not have any psychiatric diagnosis related to hospital care.

The permissions to use register data and link diagnostic data to YFS data were acquired from the respective organizations. The Ethics Committee of the Hospital District of Southwest Finland has approved the protocol.

2.2. Clinical characteristics

Height and weight of the children and adolescents were measured during the follow-ups in 1980, 1983 and 1986 and BMI was calculated as kg/m^2. BMI was categorized using the classification provided by Cole et al., with underweight representing adult BMI ≤ 18.5 kg/m^2 (Cole et al., 2007), normal weight representing adult BMI > 18.5 kg/m^2 and <25 kg/m^2 and overweight representing adult BMI ≥ 25 kg/m^2 (Cole et al., 2000). Birthweight was asked in 1983 and 1986 in a questionnaire for the participants' parents. Birthweight was further dichotomized to low birthweight representing birthweight < 2500 g vs. higher. Parents' mental disorders or problems, diagnosed by a doctor, were asked from participants' parents with a questionnaire in 1980 and 1983.

2.3. Statistical methods

The descriptive statistics are given as n (%) in total and distribution to underweight, normal weight and overweight (Supplemental table 1, Fig. 1). Associations of underweight or overweight with the risk of adult age psychosis are given as risk ratios with 95% confidence intervals (RR [95% CI]) from univariate and multivariable modified Poisson regression models (Zou, 2004). Generalized estimation equations were used in analyses of repeated measures (Zou and Donner, 2013). The Bonferroni correction was used to control for type I error in multiple testing. All multivariable models included sex, age and low birthweight (≤2500 g) as covariates. Mother's mental disorders were included in the analyses except for substance-related disorders, because in this diagnostic group there were no participants whose mother had a mental disorder. BMI data were used from all available time points and analyzed longitudinally. Statistical analyses were done using SAS® version 9.4 (SAS Institute, Cary, NC, USA) and IBM® SPSS® Statistics version 23 (IBM Corp., Armonk, NY, USA).

3. Results

The proportion of underweight was consistently larger through ages 3 to 18 years in the group of later non-affective psychosis than controls with no psychiatric diagnosis (Fig. 1, Supplemental table 1). Underweight in childhood or adolescence independently predicted later development of non-affective psychosis, increasing the covariate-adjusted risk of psychosis to two-fold (Table 1). Results were similar for schizophrenia; underweight was associated with nearly 2.5-fold risk of schizophrenia. Underweight or overweight in childhood and adolescence was not significantly associated with later affective disorder (Table 1). There was no significant association between under- or overweight in childhood and/or adolescence and later development of personality disorder ($p > 0.5$ in all analyses) or substance-related disorder ($p > 0.6$ in all analyses) (data not shown). However, the results in these two groups should be interpreted with caution due to low number

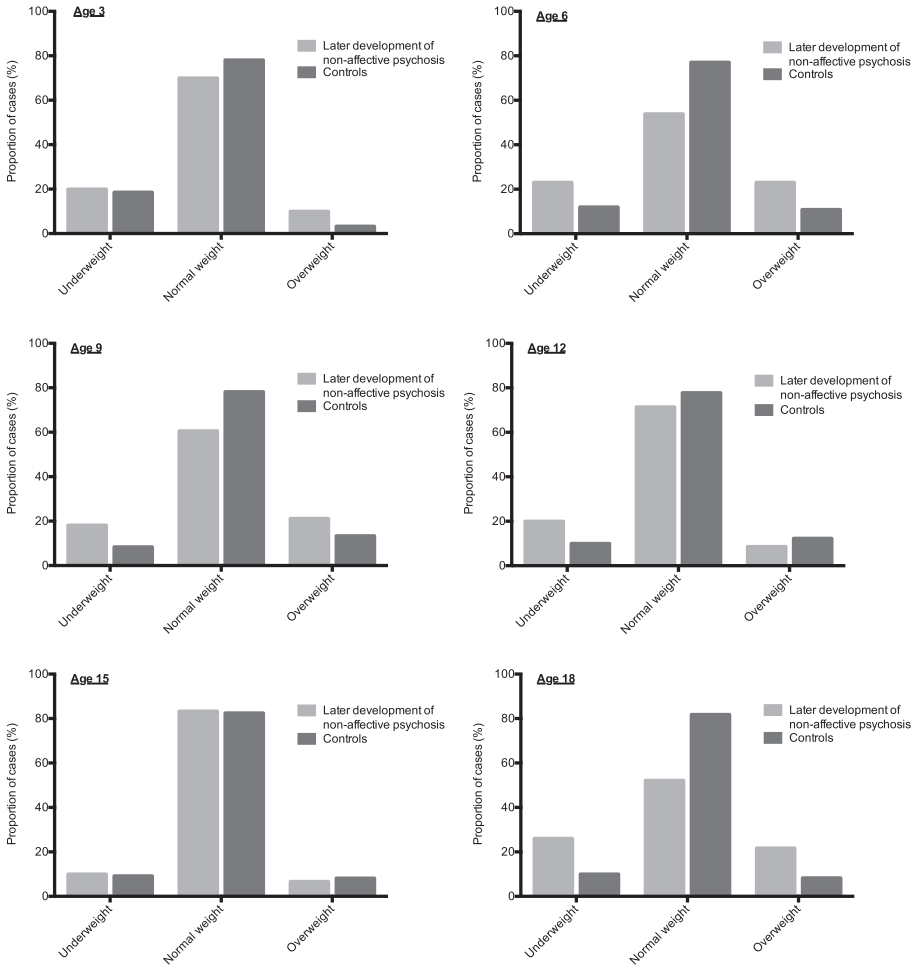

Fig. 1. Distribution of BMI using the classification provided by Cole et al. (Cole et al., 2007; Cole et al., 2000) in childhood and adolescence (3–18 years, during years 1980–1986) in the groups of later development of non-affective psychosis (DSM-IV 295, 297, 298) and controls with no psychiatric diagnoses during follow-up years 1980–2014.

of participants at each follow-up time point and limited amount of repeated measurements of the same individual.

Low birthweight (<2500 g) was significantly associated with the risk of non-affective psychosis ((RR) [95% CI] 2.04 [1.2–3.6]) in univariate analysis, but not with the risk of schizophrenia. When adjusted for BMI in childhood and adolescence, the association did not remain statistically significant. Sex was not associated with later development of non-affective psychosis or schizophrenia. Mother's mental disorders were significantly associated with the risk of non-affective psychosis (5.91 [2.5–14.0] $p < 0.001$) and schizophrenia (7.00 [2.4–20.6] $p < 0.001$) and the results remained significant after adjusting for BMI in childhood and adolescence (for psychosis 6.15 [2.5–15.2] $p < 0.001$ and for schizophrenia 6.57 [2.1–20.6] $p = 0.002$).

The association between underweight in childhood and adolescence and future psychosis or schizophrenia was stronger in multivariate analysis including all three covariates (Table 1). When covariates were added to the model one by one, sex and mother's mental disorders strengthened the association between childhood and adolescence underweight and future non-affective psychosis (underweight alone: $p = 0.013$; adjusted by sex $p = 0.009$; adjusted by mother's disorders $p = 0.009$). When low birthweight was added to the model, the association was found to be weaker but still statistically significant ($p = 0.016$). The results were similar for schizophrenia ($p = 0.055$ for underweight alone; $p = 0.044$, $p = 0.048$ and $p = 0.064$ for sex, mother's disorders and low birthweight; respectively). Any of these covariates did not affect to the results on overweight in childhood and adolescence and the risk of non-affective psychosis or schizophrenia.

Table 1
Childhood and adolescent body mass index measured at the age of 3 to 18 and their associations with the risk of later development of any non-affective psychosis, schizophrenia and affective disorders in 1980–2014.

Psychiatric diagnosis			Underweight vs. normal weight						Overweight vs. normal weight					
	Total		Univariate			Multivariate[a]			Univariate			Multivariate[a]		
	n	(%)	RR	(95% CI[b])	P[b]	RR	(95% CI[b])	P[b]	RR	(95% CI[b])	P[b]	RR	(95% CI[b])	P[b]
All non-affective psychosis	69	(1.92)	2.15	(1.1–4.1)	0.013	2.31	(1.2–4.4)	0.008	1.67	(0.8–3.3)	0.191	1.65	(0.8–3.4)	0.234
Schizophrenia	41	(1.14)	2.25	(0.99–5.1)	0.055	2.44	(1.03–5.8)	0.041	2.11	(0.9–4.9)	0.093	2.25	(0.98–5.2)	0.059
Affective disorders	112	(3.12)	1.47	(0.8–2.6)	0.127	1.45	(0.8–2.6)	0.150	0.67	(0.3–1.4)	0.229	0.68	(0.3–1.4)	0.253

RR = Risk ratio; CI = confidence interval.
[a] Multivariate analyses include age, sex, low birth weight and mother's mental disorders.
[b] Bonferroni corrected confidence intervals and p-values.

4. Discussion

4.1. General discussion

This study examined the effect of body mass index trajectories, especially deviation from normal weight, from early childhood to adolescence to the risk of non-affective psychosis and affective disorders. The main finding of this study is that underweight in childhood and adolescence independently increases the risk of schizophrenia and other non-affective psychoses, but no affective disorders, over two-fold. The effect is seen throughout childhood, although it appeared less pronounced in children at the age of 3. This may be due to a small number of subjects at that age who later developed non-affective psychosis. These results are consistent with earlier findings in other studies with reported associations between schizophrenia or other non-affective psychosis and low BMI during childhood (Sørensen et al., 2016; Wahlbeck et al., 2001) or adolescence/early adulthood (Gunnell et al., 2005; Sørensen et al., 2006; Weiser et al., 2004; Zammit et al., 2007). Our results support the idea that non-affective psychoses are not only brain disorders, but also systemic disorders with early metabolic aberrations. A link between early metabolic and structural as well as functional brain changes seems likely and is supported by neuroimaging studies (Moser et al., 2018). However, direct imaging studies with simultaneous metabolic assessments in children later developing psychosis are currently not available.

Underweight in childhood and adolescence can be hypothesized to relate to increased amount of physical activity. In the YFS cohort, physical activity index was not available before the age of 9 and, therefore, could not be used as a potential confounder in the analysis. However, we have previously reported, in the same study group, decreased levels of physical activity among 9 to 18 years old children and adolescents, who later developed non-affective psychosis (Sormunen et al., 2017). These results are somewhat surprising, because generally low physical activity increases the risk of obesity, not underweight, in children (Jiménez-Paýn et al., 2010).

Some recent studies suggest overlapping pathophysiology, e.g. family history (Mortensen et al., 2010), genetic susceptibility (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) and brain morphology (Goodkind et al., 2015) of wide range of psychiatric diseases, including schizophrenia. In fact, low birthweight is a risk factor for both schizophrenia (Abel et al., 2010) and depression (Gale and Martyn, 2004; Thompson et al., 2001). We did not find a significant association between underweight in childhood and adolescence and later development of affective disorders, with a more severe clinical phenotype that required hospital treatment. There are very few previous studies concerning underweight in childhood or adolescence and the risk of mental disorders other than psychosis. However, some studies concerning childhood overweight and risk of other mental disorders than psychosis have been published. Results from an Australian cohort study suggest that overweight at the age of 7 to 15 years increases the risk for mood disorder later in life, but not anxiety or substance use disorders (Sanderson et al., 2011). Similarly, in the Northern Finland 1966 Birth Cohort, obesity at age 14 was associated with depressive symptoms at age 31 (Herva et al., 2006). The Children in the Community Study from the USA found that obesity in adolescents aged 12–18 predicted depression and anxiety disorders in women, but not men (Anderson et al., 2007). In our study, overweight in childhood and adolescence did not predict any studied psychiatric disorder. Despite low birthweight predicting both schizophrenia (Abel et al., 2010) and depression (Gale and Martyn, 2004; Thompson et al., 2001), future patients with depression seem to gain weight normally in childhood or even become overweight, when future patients with schizophrenia remain underweight. Our results indicate that the mechanism of underweight in childhood or adolescence is specific to non-affective psychosis.

A trajectory of developing schizophrenia seems to begin already in early childhood or even before birth (Insel, 2010). Childhood underweight can be seen as one of the early markers of this process. Many genetic or nutritional factors affect growth during childhood. One putative mechanism for underweight in children who will later develop psychosis is a low level of insulin-like growth factor-I (IGF-I) (Gunnell and Holly, 2004). Low IGF-I levels are associated with low birthweight (Ong et al., 2000), low BMI and short stature (Juul et al., 1994), which are also associated with the risk of schizophrenia (Abel et al., 2010; Wahlbeck et al., 2001; Zammit et al., 2007). IGF-I crosses the blood-brain barrier and is thought to influence development and maturation of central nervous system, cellular plasticity (Dyer et al., 2016) and cognitive functioning (Aleman and Torres-Alemán, 2009). Findings about IGF-I levels in drug-naïve patients with schizophrenia have been inconsistent (Petrikis et al., 2016; Venkatasubramanian et al., 2010), but still indicative of IGF-I having a role in the pathophysiology of psychosis. Some results show elevation of serum IGF-1 due to antipsychotic treatment (Venkatasubramanian et al., 2010).

4.2. Strengths and limitations

The main strengths of this cohort study include its longitudinal and observational design and follow-up from childhood to young adulthood, before any evidence of a psychotic disorder. A full-scale follow-up of one participant was possible only for 6 years and, therefore, none of the subject data are complete from age 3 to 18. However, we have no reason to assume any remarkable differences between the birth cohorts, and the number of participants is high. We can assume a good coverage of the real prevalence of the hospital-treated disorders among the participants at adult age, as the psychiatric diagnoses were not inquired from the patients themselves but derived from the official Care Register for Health Care. The diagnostic validity for schizophrenia has been reported to be good in register-based studies (Mäkikyrö et al., 1998; Suvisaari et al., 1999), but validity of other diagnoses has not been well documented, which is a clear limitation of this study. It is clear that, in diagnostic groups other than psychosis, patients requiring hospital treatment represent more severe forms of these disorders. One limitation in this study is, that the number of subjects with future psychosis, and especially schizophrenia, is relatively low. Despite the small group sizes, the longitudinal design, low drop-out percentage and the usage of several measurements for each participant increases the statistical power in the analyses and makes this sample valuable.

4.3. Conclusions

In conclusion, underweight in childhood and adolescence is an independent risk factor for later non-affective psychosis, but not for affective disorders. These results support the hypothesis of non-affective psychosis as a neurodevelopmental disorder with early manifestations of somatic/metabolic deviations. These results have relevance for etiologic research of psychoses but also for the risk of later metabolic problems in this patient group.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.10.025.

Contributors

Authors JH, RKRS, JV and OR were responsible for the study design. NHK was responsible for the childhood and adolescence clinical characteristics. ES managed the literature searches, wrote the first draft of the manuscript and did the analyses. MMS was responsible for the statistical methods. All authors revised the manuscript and have approved the final version for publication.

Funding

The Cardiovascular Risk in Young Finns Study has been financially supported by the Academy of Finland: grants 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117797 (Gendi), and 41071 (Skidi), the Social Insurance Institution of Finland, Kuopio University Hospital, Tampere University Hospital and Turku University Hospital Medical Funds, Juho Vainio Foundation, Sigrid Jusélius Foundation, Yrjö Jahnsson Foundation, Paavo Nurmi Foundation, Finnish Foundation for Cardiovascular Research and Finnish Cultural Foundation, Tampere Tuberculosis Foundation, and Emil Aaltonen Foundation.

Conflicts of interests

None.

Acknowledgements

The authors wish to thank MSc Ville Aalto and MSSc Irina Lisinen for data management, the participants in the YFS, and YFS researchers.

References

Abel, K.M., Wicks, S., Susser, E.S., Dalman, C., Pedersen, M.G., Mortensen, P.B., Webb, R.T., 2010. Birth weight, schizophrenia, and adult mental disorder. Arch. Gen. Psychiatry 67, 923. https://doi.org/10.1001/archgenpsychiatry.2010.100.

Aleman, A., Torres-Alemán, I., 2009. Circulating insulin-like growth factor I and cognitive function: neuromodulation throughout the lifespan. Prog. Neurobiol. 89, 256–265. https://doi.org/10.1016/j.pneurobio.2009.07.008.

Anderson, S.E., Cohen, P., Naumova, E.N., Jacques, P.F., Must, A., 2007. Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: prospective evidence. Psychosom. Med. 69, 740–747. https://doi.org/10.1097/PSY.0b013e31815580b4.

Cole, T.J., C, B., Flegal, K.M., H, D.W., 2000. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320, 1240. https://doi.org/10.1136/bmj.320.7244.1240.

Cole, T.J., Flegal, K.M., Nicholls, D., Jackson, A.A., 2007. Body mass index cut offs to define thinness in children and adolescents: international survey. BMJ 335, 194. https://doi.org/10.1136/bmj.39238.399444.55.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat. Genet. 45, 984–994. https://doi.org/10.1038/ng.2711.

Dyer, A.H., Vahdatpour, C., Sanfeliu, A., Tropea, D., 2016. The role of Insulin-like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience 325, 89–99. https://doi.org/10.1016/j.neuroscience.2016.03.056.

Gale, C.R., Martyn, C.N., 2004. Birth weight and later risk of depression in a national birth cohort. Br. J. Psychiatry 184, 28–33.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., Grieve, S.M., Galatzer-Levy, I., Fox, P.T., Etkin, A., 2015. Identification of a common neurobiological substrate for mental illness. JAMA Psychiat. 72, 305–315. https://doi.org/10.1001/jamapsychiatry.2014.2206.

Gunnell, D., Holly, J.M.P., 2004. Hypothesis: do insulin-like growth factors underlie associations of birth complications, fetal and pre-adult growth with schizophrenia? Schizophr. Res. 71, 191–193. https://doi.org/10.1016/S0920-9964(03)00224-X.

Gunnell, D., Rasmussen, F., Fouskakis, D., Tynelius, P., Harrison, G., 2003. Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. Am. J. Epidemiol. 158, 291–300. https://doi.org/10.1093/aje/kwg118.

Gunnell, D., Harrison, G., Whitley, E., Lewis, G., Tynelius, P., Rasmussen, F., 2005. The association of fetal and childhood growth with risk of schizophrenia. Cohort study of 720,000 Swedish men and women. Schizophr. Res. 79, 315–322. https://doi.org/10.1016/j.schres.2005.07.022.

Herva, A., Laitinen, J., Miettunen, J., Veijola, J., Karvonen, J.T., Läksy, K., Joukamaa, M., 2006. Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. Int. J. Obes. 30, 520–527. https://doi.org/10.1038/sj.ijo.0803174.

Insel, T.R., 2010. Rethinking schizophrenia. Nature 468, 187–193. https://doi.org/10.1038/nature09552.

Jiménez-Paín, D., Kelly, J., Reilly, J.J., 2010. Associations between objectively measured habitual physical activity and adiposity in children and adolescents: systematic review. Int. J. Pediatr. Obes. 5, 3–18. https://doi.org/10.3109/17477160903067601.

Jones, P., Rodgers, B., Murray, R., Marmot, M., 1994. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 344, 1398–1402. https://doi.org/10.1016/S0140-6736(94)90569-X.

Juul, A., Bang, P., Hertel, N.T., Main, K., Dalgaard, P., Jørgensen, K., Müller, J., Hall, K., Skakkebaek, N.E., 1994. Serum insulin- like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. J. Clin. Endocrinol. Metab. 78, 744–752.

Mäkikyrö, T., Isohanni, M., Moring, J., Hakko, H., Hovatta, I., Lönnqvist, J., 1998. Accuracy of register-based schizophrenia diagnoses in a genetic study. Eur. Psychiatry 13, 57–62. https://doi.org/10.1016/S0924-9338(98)80019-9.

Mortensen, P.B., Pedersen, M.G., Pedersen, C.B., 2010. Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? Psychol. Med. 40, 201–210. https://doi.org/10.1017/S0033291709990419.

Moser, D.A., Doucet, G.E., Lee, W.H., Rasgon, A., Krinsky, H., Leibu, E., Ing, A., Schumann, G., Rasgon, N., Frangou, S., 2018. Multivariate associations among behavioral, clinical, and multimodal imaging phenotypes in patients with psychosis. JAMA Psychiat. https://doi.org/10.1001/jamapsychiatry.2017.4741.

Ong, K., Kratzch, J., Kiess, W., Costello, M., Scott, C., Dunger, D., 2000. Size at birth and cord blood levels of insulin, Insulin-like Growth Factor I (IGF-I), IGF-II, IGF-Binding Protein-1 (IGFBP-1), IGFBP-3, and the soluble IGF-II/mannose-6-phosphate receptor in term human infants. J. Clin. Endocrinol. Metab. 85, 4266–4269.

Petrikis, P., Boumba, V.A., Tzallas, A.T., Voulgari, P.V., Archimandriti, D.T., Skapinakis, P., Mavreas, V., 2016. Elevated levels of Insulin-like Growth Factor-1 (IGF-1) in drug-naïve patients with psychosis. Psychiatry Res. 246, 348–352. https://doi.org/10.1016/j.psychres.2016.09.053.

Raitakari, O.T., Juonala, M., Rönnemaa, T., Keltikangas-Järvinen, L., Räsänen, L., Pietikäinen, M., Hutri-Kähönen, N., Taittonen, L., Jokinen, E., Marniemi, J., Jula, A., Telama, R., Kähönen, M., Lehtimäki, T., Åkerblom, H.K., Viikari, J.S.A., 2008. Cohort profile: the cardiovascular risk in young Finns study. Int. J. Epidemiol. 37, 1220–1226. https://doi.org/10.1093/ije/dym225.

Sanderson, K., Patton, G.C., McKercher, C., Dwyer, T., Venn, A.J., 2011. Overweight and obesity in childhood and risk of mental disorder: a 20-year cohort study. Aust. New Zeal. J. Psychiatry 45, 384–392. https://doi.org/10.3109/00048674.2011.570309.

Sørensen, H.J., Mortensen, E.L., Reinisch, J.M., Mednick, S.A., 2006. Height, weight and body mass index in early adulthood and risk of schizophrenia. Acta Psychiatr. Scand. 114, 49–54. https://doi.org/10.1111/j.1600-0447.2006.00784.x.

Sørensen, H.J., Gamborg, M., Sørensen, T.I.A., Baker, J.L., Mortensen, E.L., 2016. Childhood body mass index and risk of schizophrenia in relation to childhood age, sex and age of first contact with schizophrenia. Eur. Psychiatry 34, 64–69. https://doi.org/10.1016/j.eurpsy.2016.01.2425.

Sormunen, E., Saarinen, M.M., Salokangas, R.K.R., Telama, R., Hutri-Kähönen, N., Tammelin, T., Viikari, J., Raitakari, O., Hietala, J., 2017. Effects of childhood and adolescence physical activity patterns on psychosis risk—a general population cohort study. NPJ Schizophr. 3, 5. https://doi.org/10.1038/s41537-016-0007-z.

Suvisaari, J.M., Haukka, J.K., Tanskanen, A.J., Lönnqvist, J.K., 1999. Decline in the incidence of schizophrenia in Finnish cohorts born from 1954 to 1965. Arch. Gen. Psychiatry 56, 733–740. https://doi.org/10.1001/archpsyc.56.8.733.

Thompson, C., Syddall, H., Rodin, I., Osmond, C., Barker, D.J.P., 2001. Birth weight and the risk of depressive disorder in late life. Br. J. Psychiatry 179, 450–455. https://doi.org/10.1192/bjp.179.5.450.

Venkatasubramanian, G., Chittiprol, S., Neelakantachar, N., Shetty, T., Gangadhar, B.N., 2010. Effect of antipsychotic treatment on Insulin-like Growth Factor-1 and cortisol in schizophrenia: a longitudinal study. Schizophr. Res. 119, 131–137. https://doi.org/10.1016/j.schres.2010.01.033.

Wahlbeck, K., Forsén, T., Osmond, C., Barker, D.J.P., Eriksson, J.G., 2001. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. Arch. Gen. Psychiatry 58, 48–52. https://doi.org/10.1001/archpsyc.58.1.48.

Weiser, M., Knobler, H., Lubin, G., Nahon, D., Kravitz, E., Caspi, A., Noy, S., Knobler, H.Y., Davidson, M., 2004. Body mass index and future schizophrenia in Israeli male adolescents. J. Clin. Psychiatry 65, 1546–1549. https://doi.org/10.4088/JCP.v65n1117.

Wyatt, R.J., Henter, I.D., Mojtabai, R., Bartko, J.J., 2003. Height, weight and body mass index (BMI) in psychiatrically ill US Armed Forces personnel. Psychol. Med. 33, 363–368. https://doi.org/10.1017/s0033291702006694.

Zammit, S., Rasmussen, F., Farahmand, B., Gunnell, D., Lewis, G., Tynelius, P., Brobert, G.P., 2007. Height and body mass index in young adulthood and risk of schizophrenia: a longitudinal study of 1 347 520 Swedish men. Acta Psychiatr. Scand. 116, 378–385. https://doi.org/10.1111/j.1600-0447.2007.01063.x.

Zou, G., 2004. A modified Poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. 159, 702–706. https://doi.org/10.1093/aje/kwh090.

Zou, G., Donner, A., 2013. Extension of the modified Poisson regression model to prospective studies with correlated binary data. Stat. Methods Med. Res. 22, 661–670. https://doi.org/10.1177/0962280211427759.