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Review Article

The Impact of Familial Predisposition to Obesity and Cardiovascular Disease on Childhood Obesity

Louise Aas Nielsen^a Tenna Ruest Haarmark Nielsen^{a, b}
Jens-Christian Holm^{a, b, c}

^aThe Children's Obesity Clinic, Department of Paediatrics, Copenhagen University Hospital Holbæk, Holbæk, Denmark; ^bNovo Nordisk Foundation Centre for Basic Metabolic Research, Section of Metabolic Genetics, University of Copenhagen, Copenhagen, Denmark; ^cUniversity of Copenhagen, Faculty of Health and Medical Sciences, Copenhagen, Denmark

Key Words

Pediatric obesity · Familial predisposition · Cardiovascular diseases · Diabetes mellitus type 2

Abstract

The prevalence of childhood obesity has reached alarming rates world-wide. The aetiology seems to be an interplay between genetic and environmental factors, and a surrogate measure of this complex interaction is suggested as familial predisposition. Familial predisposition to obesity and related cardiovascular disease (CVD) complications constitute the presence of obesity and/or obesity-related complications in primarily blood-related family members. The approaches of its measurement and applicability vary, and the evidence especially of its influence on obesity and obesity treatment in childhood is limited. Studies have linked a familial predisposition of obesity, CVD (hypertension, dyslipidaemia and thromboembolic events), and type 2 diabetes mellitus to BMI as well as other adiposity measures in children, suggesting degrees of familial aggregation of metabolic derangements. A pattern of predispositions arising from mothers, parents or grandparents as being most influential have been found, but further comprehensive studies are needed in order to specify the exact implications of familial predisposition. In the scope of childhood obesity this article reviews the current literature regarding familial predisposition to obesity and obesity-related complications, and how these familial predispositions may impact obesity in the offspring.

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Louise Aas Nielsen, MS.
The Children's Obesity Clinic, Department of Paediatrics
Copenhagen University Hospital Holbæk
4300 Holbæk, Denmark
loani@regionsjaelland.dk

Introduction

Childhood obesity has been increasing with an alarming rate during the last decades. The World Health Organization (WHO) currently estimates that 42 million children under the age of 5 years are obese [1]. This development causes great concern, even though recent studies suggest that prevalence rates have reached a plateau [2, 3].

Obesity is associated with a great variety of somatic and psychosocial co-morbidities including severe metabolic and cardiovascular complications, which normally are associated with adulthood. Driven largely by insulin resistance, obesity pathophysiologically induces a metabolically deranged state in a majority of obese children, causing dyslipidaemia in 27% of obese children [4], hypertension in up to 50% [5], steatosis in 31% [6] and impaired glucose metabolism in 17% [7]. In the relative absence of effective prevention and intervention, obese children and adolescents increase their risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD), including coronary heart disease, in adulthood – conditions which are associated with premature deaths [8–11].

The aetiology of childhood obesity can partially be ascribed to specific known and unknown genetic variants and a global drift toward an obesogenic lifestyle characterised by sedentary behaviour and a calorie-dense food intake. Altogether, the aetiology seems to be an interplay between genetic and environmental contributors. Thus, the family surrounding the child is an important contributor since they share genes, behaviour and environment. This phenomenon is known as familial predisposition. The objective of this article is to review the current literature on familial predisposition and its relation to childhood obesity that is available at the PubMed database.

Familial Predisposition

What Is Familial Predisposition?

Familial predisposition comprises how the occurrence of a specific disorder in blood-related family members predisposes a patient to the same or similar disorders. The number of affected family members may represent to which extent there is a risk for a given individual to develop family-prone disorders. In the field of cardiology, familial predisposition is a well-defined designation, referred to as a ‘family history’, and a family history of CVD has been proposed as an independent CVD risk factor [12].

Given that paediatric patients share genes, and usually environment, with their family members, familial predisposition may, as described in behavioural genetics, operate as a surrogate measure of the complex interplay between genetic and environmental factors [13, 14]. For both researchers and clinicians this approach may be beneficial in the struggle against childhood obesity; partly because it supports current knowledge regarding the aetiology of childhood obesity, and partly because familial predisposition potentially could be used as a tool to predict treatment outcomes.

Genetic-Environmental Interplay in Obesity

In the research of obesity, a variance of acquisition and accumulation of fat has been observed among populations [15]. In order to understand this mechanism, studies have been designed to estimate the heritability of obesity, i.e., the proportion of the phenotype variation which can be explained by genetic factors. At present, 97 genetic loci have been shown to be associated with BMI, which is a relative imprecise measure of obesity, and 188 loci have been identified to be associated with obesity-related phenotypes [16]. However, the effect sizes of the individual loci are in general small and do not offer any direct explanation of either the prevalence or the degree of obesity [16].

Heritability studies of monozygotic twins have observed that monozygotic twins, as compared to dizygotic twins, are more alike in their acquisition of fat, suggesting that the adaptation to an altered energy balance is highly influenced by the genotype [17–19]. Other heritability studies, which in addition to monozygotic twins involve adopted children, have likewise identified genes as a strong determining factor for BMI. In a study of 5,092 mono- and dizygotic twin pairs, the heritability has been estimated to be 77%, which furthermore is suggested to increase with age [14, 20–22]. Beyond the genotype, the adaptive responses of the many childhood obesity phenotypes are influenced by environmental, social, behavioural, cultural, ethnic and parental factors [15, 21]. These factors include dietary intake, level of physical activity, sedentary behaviour, family structure (parental weight status, parental perception of overweight, parental feeding practices, socio-economic status and more), day care and school environment as well as influences during foetal development (i.e. intrauterine environment, maternal smoking, gestational diabetes, maternal weight) and early growth and development (i.e., birth weight, breastfeeding) [22–29]. As a consequence, this large variation in phenotypes and environmental influences challenges both clinicians and researchers in their understanding of the aetiology of non-monogenic forms of childhood obesity.

Measurement of Familial Predisposition

To understand the interplay between genetic and environmental factors, a method to measure this complexity is needed. Familial predispositions may function as a surrogate measure of the combined genetic-environmental product, but this method faces major challenges in terms of measuring methods. In general, familial predisposition constitutes a part of a substantial medical history, in which the clinician outline the occurrence of hereditary diseases as well as more common occurring diseases such as cancer, diabetes mellitus and CVD. In the scope of childhood obesity, one should consider which familial predispositions are of relevance. In spite of the fact that obesity is only declared as a disease in the USA [30], obesity constitutes a key familial predisposition, which frequently is taken into consideration due to a common understanding that obesity runs in families. Furthermore, familial predispositions to CVD and T2DM are important in the context of obesity, as both conditions exhibit a metabolically deranged state in the patients, which often is associated with an obesogenic way of living and the development of obesity.

Whilst measuring familial predispositions, another important consideration is the number of family members that should be taken into account. Some studies investigate biological parents exclusively [23, 31–34] while others also include grandparents [35–39] and siblings [23, 39, 40]. By including biological parents and siblings the diseases of first-degree relatives is covered, while grandparents are second-degree relatives. Medically, including grandparents is a good approach, partly in order to illustrate life course patterns and thus substantiate an inherited aetiology, and partly to include families in which grandparents are a part of the household. But it is a comprehensive task in the light of contemporary family constellations, which are often characterised by blended families. One might argue that, to proper illustrate the interplay between genetic and environmental factors, one should include biological family members down to second-degree relatives (genetics) as well as step-parents, half-siblings and other members of the household (contributing to the environment). Although this definition might seem too wide, we cannot exclude the significance of such influences, neither in the context of the aetiology nor regarding the treatment of childhood obesity, which is why investigations into these relationships need to be elaborated.

In analogy with the great variety of family constellations, attention to family size and the age of family members should be considered, since family size and age as confounders may contribute with variability. The age of family members is important due to a longer exposure to the obesogenic environment and/or an increased life course penetrance and thus a greater

statistical probability of developing the predisposing diseases over time. The size of the family is likewise important due to the fact that many family members are anticipated to increase the probability of emerging diseases in the family.

Furthermore, special attention should be paid to the collection of data. Researchers and clinicians may always seek to obtain the most reliable data available but, due to limitations in time and resources or the fact that familial predisposition in many studies is a secondary measure, the approaches in the literature vary. For the most part, data is collected by recruiting children directly from childcare institutions or paediatric departments, but in some studies the children are recruited through their family members exhibiting diseases [36, 40, 41]. Medical background of family members is most often registered using questionnaires; either filled out in the consultation by an interviewer [43, 44] or at home by the family themselves [23, 45]. There are obvious problems using this approach of self-reported data, which include recall bias and undiagnosed or unacknowledged illness, i.e., the inability to recognise a family member as being obese [31, 36, 37, 45]. Another possibility would be to consult the medical records of the family members [42, 46]. However, weight and height, and thus obesity, are often not registered in the medical journals, which is why objective measurement of weight, height and other adiposity measures (waist circumference (WC), skinfold thicknesses etc.) of both the child and family members may be a necessity [34, 44, 47]. In general, the most accurate measure of familial predisposition may constitute a combination of adiposity measurements, self-report, and verification of diseases and patient-specific data in medical records and/or registries [46].

Another challenge is how to take the family history into account. Some studies use a categorical approach with either a positive or a negative family history [48–50]. Other studies take into account whether one or both parents contribute [51], while others have introduced a scoring system in which first-degree relatives contribute with a higher score than second-degree relatives [52]. Altogether, the medical term familial predisposition needs a precise definition of which and how many family members are affected in order to constitute a predisposition, which may be dependent on inheritance and penetrance of the specific condition.

Familial Predisposition to Obesity

Although familial predisposition is yet to be defined, some studies have investigated how familial obesity, as a predisposing factor, influences obesity and obesity-related complications in children. The majority of the identified literature has linked parental BMI and overweight/obesity with the BMI or the risk of obesity in their offspring, in childhood as well as in adulthood.

The influence of a familial predisposition to obesity seems to be especially important in the development of obesity during early childhood. In studies of obese and non-obese children, which most often address children under the age of 10 years, parental BMI or overweight/obesity is associated with the BMI or the risk of overweight and obesity in the children, and it is shown to be an important predictor of obesity in adulthood [23, 31, 32, 53–56]. Furthermore, The 1958 British Birth Cohort study (n = 16,794, offspring n = 2,908) shows that an increased risk of overweight and obesity in the offspring is associated with increased parental BMI and a high parental BMI gain during both childhood and adulthood [57].

Likewise, overweight grandparents have been associated with BMI and increased prevalence rates of obesity in children, both dependent and independent of parental BMI [35, 36]. Also, in the offspring of bariatric surgery patients, the proportion of obesity among biological children/grandchildren is significantly greater than in non-biological children/grandchildren who share environment, but not genetics [37].

A varying influence of maternal and paternal weight status on the offspring has been observed in studies that links parental BMI to BMI and other adiposity measures of the children/adolescents. In adolescents, the risk of overweight/obesity is associated with parental BMI, but the association differs between mothers and fathers; a high paternal BMI increases the risk of overweight/obesity in both boys and girls, whereas a high maternal BMI decreases the risk of obesity among girls [58]. In contrast, a stronger influence of maternal adiposity and weight status/change on the child has been found in a small longitudinal study (n = 197) of 5- to 7-year-old girls [51] as well as in other studies that include Indian and Pima Indian children [59–61]. The greatest risk of childhood overweight/obesity however, is seen in children from families in which both parents are overweight or obese [32, 53, 59, 62].

In summary, a familial predisposition to obesity has the greatest impact on BMI in children under the age of 10 years. The majority of literature investigates parents, and overweight/obesity in mothers or both parents has been found to be the strongest contributors. Furthermore, a correlation with grandparental weight status is seen, which further underline a genetic contribution.

Familial Predisposition to Cardiovascular Disease

Tracking of CVD risk factors from childhood to adulthood is well-known [63, 64]. The fact that CVD risk factors can be identified in early life has led the American Heart Association to release a guide to prevent CVD starting in childhood [65]. But how does a positive family history of CVD, manifested as hypertension, dyslipidaemia, T2DM and thromboembolic events, affect development of obesity in the offspring?

Studies of Italian children have associated a familial predisposition to CVD (hypertension, T2DM, dyslipidaemia and thromboembolic events) with increased skinfold thickness (subscapular/triceps ratio) [55] and higher waist-to-height ratio. Furthermore, a positive family history of CVD is associated with a higher BMI in the offspring, with the highest BMI found in children of parents suffering from premature CVD [48].

In the Bogalusa Heart Study (n = 8,276), offspring of hypertensive and diabetic parents was more overweight and obese, respectively, measured as weight and skinfold thickness, irrespective of age [66]. Additionally, this study associates parental heart attack with a greater degree of overweight in pubertal children [66, 67].

Studies focusing on familial predispositions to T2DM are scarce. Apart from a study of a mixed group of Asian Indian adolescents, which directly associates familial T2DM with adiposity measures [41], the majority of studies only show a tendency of such an association. In these studies, the predisposed children show the highest proportion of overweight and obesity. Moreover a predisposition was also shown for parental diabetes and gestational diabetes in Latino children [45] and for parental and grandparental T2DM on both the maternal and paternal side in obese and non-obese Indian children and adults [39, 68]. The impact upon obesity seems to be higher if both parents are affected [42, 68]. Furthermore, adults with a normal glucose tolerance and T2DM in first-degree relatives (with maternal dominance) exhibit higher BMI and WHR [69].

Though the focus of the present review is on familial predispositions to childhood obesity, it is relevant to consider familial predispositions to CVD and CVD risk factors in the offspring as they are often defined as obesity-related complications. These risk factors include increases in diastolic and systolic blood pressure, which are particularly associated with familial hypertension [52, 66, 70], as well as alterations in the lipid [41, 42, 44, 68–72] and glucose metabolism [38, 41, 42, 46, 68, 69], which often is associated with familial T2DM and dyslipidaemia. In a recent cross-sectional study from the Bogalusa Heart Study, parent's childhood rather

than their adult BMI, blood pressure, and LDL cholesterol have been shown to be a strong predictor of the corresponding CVD risk factors of their children [73]. Altogether, these findings suggest a genetic aggregation of CVD risk factors in parents and offspring, but the impact of a familial predisposition to hypertension, T2DM, dyslipidaemia and thromboembolic events on obesity in children needs to be clarified further.

Familial Predispositions in Childhood Obesity Treatment

In the field of paediatrics, childhood obesity treatment [74, 75] has gained increased attention over the past 10 years, but the knowledge regarding the impact of familial predispositions on childhood obesity treatment is sparse. Studies have shown that children with a familial predisposition to obesity, including obesity in parents and siblings, are less inclined to succeed in weight loss programmes [40, 76–78]. Furthermore, in severely obese children, a diminished response to treatment has been associated with maternal obesity [79]. In a retrospective study looking at medical charts, parental obesity-related co-morbidities including T2DM, hypertension, dyslipidaemia and CVD have likewise been associated with a poorer response to childhood obesity treatment [80]. The strongest association is seen if both parents exhibit predispositions [80]. The interaction between parental weight changes upon childhood obesity treatment has also been investigated. By investigating a family-based ‘parent-only’ and a ‘parent-child’ approach, it is established that parental weight change is an important predictor of the treatment outcome of the children [34]. Data from our own group have shown that a familial predisposition to T2DM is associated with a higher degree of obesity at the baseline, and a familial predisposition to obesity is associated with a better response to obesity treatment in obese girls [81]. Altogether, the limited amount of literature suggests that the occurrence of familial predispositions may be associated with the treatment outcome in childhood obesity treatment.

Discussion

The present review has suggested familial predisposition to be the interplay between genetic and environmental factors, but the applicability in a clinical and/or research setting is, at present, restricted by the absence of a comprehensive and consistent definition. Such a definition should outline the number of included generations, whether non-biological family members should be included as influencing the environment and whether one should correct for family size and age of family members. In addition, the number of cases in the family that constitutes a predisposition and the most realistic and ideal measurement of familial predisposition needs to be defined.

Since the knowledge regarding familial predispositions in childhood obesity is limited, the measurement of familial predisposition should be reserved to biological family members including second-degree relatives, in order to optimise data certainty. Furthermore, at least one case, optimally in more than one generation, should be identified in the family in order to classify it as a familial predisposition. Regarding measurement, self-report is a useful tool for the clinicians, but in research it would be preferable to have the information verified by medical records, registries or objective measurements in order to minimise recall bias, neglect and ignorance of familial diseases.

An obvious question remains: how can familial predisposition be utilised? Familial predispositions can be used as a preventive measurement, in which clinicians screen children in order to detect those potentially at risk of childhood obesity or its related complications. This seems to be relevant for all familial predispositions discussed in this review, since they

correlate with BMI or other obesity measurements in the children. Another possibility is to consider familial predispositions in childhood obesity treatment. In this field, familial predispositions may serve as a tool to predict children at risk of developing obesity-related complications and thus to identify children where a specialised intervention should be initiated. Since it is unclear whether or not there is an association between familial predisposition and treatment response, this question should be addressed in future studies. Another preventive approach is to detect young children at risk of developing childhood obesity when family members with obesity and obesity-related diseases are treated [41, 42]. Furthermore, information about familial predisposition and obesity genetics in consultations of obese adults have been found to decrease self-blame about eating, suggesting that familial predisposition, besides recognition of obesity as a disease, potentially could reduce stigmatisation of obese individuals and encourage obese children to successful treatment [82].

Familial predisposition to obesity is shown to have the greatest impact on children under the age of 10, which may suggest that environmental influences increase with age. However, this is contrary to the heritability studies of adoptees and twins, which find that the heritability of obesity increase with age [21]: This outlines the importance of understanding the interplay, rather than the distinction, between genetic and environmental factors, as illustrated by the interaction between physical activity and the *FTO* gene in adults [74]. Even though no interaction between physical activity and the *FTO* gene is found in children [83], we cannot exclude the possibility that there may be some specific genes or combinations of genes which in interaction with specific environmental factors increases or decreases the development or maintenance of childhood obesity. Moreover, familial predisposition to obesity and T2DM arising from mothers, parents or grandparents tend to have the strongest influence on the degree of obesity in children. The familial predisposition from grandparents and both parents may imply a strong genetic influence, whereas the maternal dominance may be explained by prenatal and perinatal factors, which have been associated with childhood obesity [23, 26–28, 54, 56]. One may speculate whether or not these findings altogether imply that familial predisposition to obesity and obesity-related complications predispose children to develop a metabolically deranged state at a young age, which either increases their risk of developing obesity or, once they are obese, increases their risk of developing obesity-related metabolic co-morbidities.

Conclusion

In this article we have reviewed the term ‘familial predisposition’, its applicability and limitations, and, most importantly, how familial predispositions to obesity and obesity-related complications impact the development and treatment of childhood obesity. Summarising the results, familial predisposition to obesity and obesity-related complications and its impact on obesity in children is an important marker of the complex interplay between genetic and environmental factors, which could, potentially, serve as a preventive and predictive marker in the struggle against childhood obesity. However, in order to accomplish a comprehensive and realistic definition of familial predisposition, which benefits both clinicians and researchers, studies on obese children and their family members up to second-degree relatives are required, which combine self-report, objective adiposity measurements and validation in medical charts and registries.

Disclosure Statement

All authors declare no conflicts of interest

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