



Review article

Paediatric obesity and cardiovascular risk factors – A life course approach



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ARTICLE INFO

Article history:

Received 31 January 2017

Accepted 9 February 2017

Available online 17 March 2017

Keywords:

Paediatric obesity

Cardiovascular risk factors

Life course

ABSTRACT

Childhood obesity is increasingly prevalent worldwide, and Portugal presents one of the highest prevalence of obesity and overweight among the European countries. Since childhood obesity is a risk factor for obesity in adulthood, the high prevalence of overweight and obesity in paediatric age currently experienced is expected to lead to even higher prevalence of obesity in adulthood in future decades.

It is well known that the prenatal period and infancy are critical or sensitive periods for obesity development, but a growing body of evidence also suggests a relevant role of childhood and adolescence. The exposure to some factors during these periods or specific time frames within these periods may confer additional risk for obesity development.

Paediatric obesity is associated with cardiovascular risk factors both in the short or medium-term, but also in the long term, conferring additional risk for future adult health. However, it is not clear whether the relation between paediatric obesity and adult health is independent of adult adiposity. There is a moderate to high tracking of obesity from paediatric age into adulthood, which may partially explain the association with adult outcomes. Therefore, there has been increasing interest on life course frameworks to study the effect of the dynamics of adiposity across paediatric age on adult outcomes, namely on the cardiovascular disease risk. The use of this approach to study determinants and consequences of obesity raises methodological challenges to summarize the exposure to adiposity/obesity across the life span, being the identification of growth trajectories and the quantification of the duration of obesity among the most used methods. However, further investigation is still needed to explore the best methods to summarize exposure to adiposity and its variation across time.

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Paediatric obesity

Prevalence and trends

High prevalence of obesity is a major public health concern and obesity is acknowledged as a global pandemic.¹ The Global Burden of Disease (GBD) Study 2013 reported an increase in worldwide prevalence of overweight and obesity between 1980 and 2013.² The GBD Study 2013 used data from surveys, reports, and published studies with physical measurements or self-reported height and weight, and presents detailed estimates of overweight and obesity by region and country, for both children and adults.² Data from this report estimated 2.1 billion overweight and obese individuals

worldwide in 2013, reflecting the rise of 27.5% in the prevalence of overweight and obesity in adults and of 47.1% in children in the period from 1980 and 2013.² The rate of increase was higher from 1992 to 2002, and slowed down in the past decade, particularly in developed countries, but prevalence is still increasing in most countries.²

Considering the age strata, the analysis of trends in obesity prevalence over successive birth cohorts showed that the most rapid weight gains have occurred in the age group of 20–40 years, in both developed and developing countries, and that peak prevalence of obesity was moving to younger ages in developed countries.² Prevalence of obesity in paediatric age has markedly increased since 1980, in particular in developed countries: from 1980 to 2013 it increased from 16.9% to 23.8% in boys, and from 16.2% to 22.6% in girls.² In Portugal, information on national data on paediatric obesity collected by routine is scarce and surveillance initiatives on childhood obesity have been implemented just in recent years.³ Estimates from the GBD Study 2013 using secondary

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data sources reported for Portugal 28.7% of overweight and obesity in children and adolescents (<20 years) for boys and 27.1% for girls, which is above the average estimate for the Western Europe: 24.2% and 22.0%, respectively.² The WHO European Childhood Obesity Surveillance Initiative (COSI) was established in 16 countries to measure trends in overweight and obesity in children aged 6.0–9.0 years.⁴ Data collected in this context showed that Portugal was one of the European countries presenting the highest prevalence of obesity and overweight.⁴ In 2007/2008 prevalence of overweight (>1 z-score, according to WHO growth reference) was 40.5% in 7-year-old boys and 35.5% in girls; the respective estimates in 2009/2010 were 31.5% and 36.2%.⁴ A previous cross-sectional national study developed in 2002/2003 had reported 20.3% of overweight (excluding obesity) and 11.3% of obese children aged 7–9.5 years, but using the IOTF criteria.⁵

For Portuguese adolescents, repeated national data on obesity is available from the Health Behaviour in School-aged Children (HBSC), a WHO cross-national survey conducted every four years in 44 countries and regions across Europe and North America.⁶ The self-reported data showed that among Portuguese adolescents from the 6th, 8th and 10th grades there was 18.2% of overweight and obesity combined in 2014, according to the IOTF reference, and prevalence was higher in boys.⁷ The comparison with previous HBSC surveys showed stable estimates of overweight and obesity since 2002.^{7,8}

Objectively measured data on weight and height of adolescents is not collected at the national level in Portugal, on a regular basis. Only cross-sectional studies are available at national level in adolescents, and some cross-sectional or cohort studies at regional or local level. A national cross-sectional school-based study in 2008 including over 22,000 children and adolescents aged 10–18 years of age, found 17.4% of overweight and 5.2% of obesity, according to IOTF cut-offs.⁹ A review on obesity in Portuguese children and adolescents published in 2011, which included studies since 2007 from specific regions or communities, reported estimates based on IOTF cut-offs ranging from 13.4% to 28.6% in males and from 8.8% to 25.6% in females for overweight for adolescents (10–19 years); estimates for obesity varied between 3.2% and 13.0% in males, and from 0.6% and 5.8% in females.¹⁰ Longitudinal data is scarce, but in the EPITeen cohort, which recruited 13-year-old adolescents enrolled at schools of Porto in 2003/2004, the prevalence of obesity at the baseline was 11.3% in boys and 9.2% in girls and the prevalence of overweight 16.9% and 16.0% respectively for boys and girls, according to the CDC reference.¹¹ Data from the follow-up of participants showed a mean decrease in the body mass index (BMI) z-score between 13 and 17 years, resulting in a decrease in the prevalence of obesity to 7.8% in boys and 3.8% in girls.¹²

Although the lack of harmonized, objectively measured data, and collected on a regular basis on obesity in paediatric age in Portugal, available data suggest that Portugal presents one of the highest prevalence of paediatric obesity and overweight among the European countries.^{2,4} Since childhood obesity is a risk factor for obesity in adulthood, the high prevalence of overweight and obesity in paediatric age currently experienced by our country, as well as in most countries, is expected to lead to an even higher prevalence of obesity in adulthood in future years and decades.^{13,14}

Critical and sensitive periods for obesity development

A growing body of evidence shows that there are critical or sensitive periods across the life course for obesity development.^{15–17} Critical periods refer to specific stages of the development during which exposure to specific environmental stimuli may confer permanent anatomical or functioning changes with consequences for long-term effects of specific outcomes.^{16,18,19} These are specific time frames, during which exposures may confer increased

risk of disease, but outside those time frames exposure to those factors do not confer additional risk of disease. A sensitive period refers to time frames of also rapid development, during which a greater effect of exposure to some factor is stronger in comparison to exposure outside that period, but that effect may be modified or reversed.^{18,19}

Foetal life is an example of a critical period, since tissues and organs systems undergo profound development and exposure to specific factors may irreversibly “programme” physiological functioning, playing an important role in disease aetiology.^{16,20,21} Adolescence, on the other hand, may be considered a sensitive period since a range of different developmental stages occur at variable time periods, and a specific critical period may not exist. However, in the literature the prenatal period, infancy, childhood and also adolescence are all usually identified as critical periods for obesity development.

Prenatal period and infancy

Regarding the prenatal period and infancy, observations that maternal nutrition could impact on offspring obesity were firstly described in the Dutch Hunger Winter Study in the 1970s.²² This study showed that 19-year-old males who had been exposed to famine in the first two trimesters of gestation, due to severe food rationing imposed in the winter and spring 1944–1945 during the Second World War, had higher prevalence of obesity, in comparison to those exposed in the other trimesters.²² Later epidemiological studies by Barker et al.^{23–25} on the association between rates of infant mortality and adult deaths (ecological analysis) and on the association between birthweight and adult mortality from ischaemic heart disease conducted to the developmental origins theory, also known as the “Barker’s hypothesis”.²⁶ This theory suggests that undernutrition during gestation may lead to foetal programming that changes body’s structure, function, and metabolism with implication in the aetiology of adult coronary heart disease.²⁶ This theory was later expanded to the Developmental Origins of Health and Disease (DOHaD)^{27,28} incorporating the effect of broader environmental exposures (nutrition, environmental chemicals, drugs, infections, or stress), not only in pregnancy but also in preconception period and in infancy, due to developmental plasticity, on widespread consequences for later health including obesity. In line with this theory several studies have shown that factors such as maternal obesity, nutrition and stress, exposure to chemicals during pregnancy and rapid post-natal weight gain are associated with obesity.^{29,30} Mechanisms might include epigenetic processes, such as DNA methylation, that alter gene expression and increase susceptibility for later disease, but also shared social influences across generations.^{19,29,30} The inter-generational effects of disease susceptibility seems not to be restricted to one generation, since some studies have shown associations across at least three generations.³¹

Childhood

Adiposity rebound occurring at mid-childhood is also acknowledged as a critical period for obesity development.^{15,16} Adiposity increases during the first year of life, and then a decline is observed until a minimum (nadir) reached at approximately 6 years of age; the increase in adiposity registered after that nadir was firstly described as adiposity rebound by Rolland-Cachera et al.³² The timing of the adiposity rebound was shown to predict later adiposity levels; the earlier the age of adiposity rebound, the greater the degree of adiposity in adolescence and in young adulthood.^{32,33} Several studies have replicated the findings on the association between early adiposity rebound and obesity later in life.^{16,34} As shown by Taylor et al., the difference in BMI at 18–21 years can be around 3 BMI units higher for those with early adiposity rebound (<5 years), compared to those with late rebound (>7 years).³⁴

However, the utility of adiposity rebound for the prediction of later adiposity is controversial, since the rebound is identified based on at least 3 serial BMI measurements, meaning that it can only be identified after its occurrence. Additionally, adiposity rebound is based on BMI changes, which may not represent real changes in body fat.^{34,35} Reverse causation may also be a possible explanation for the association between timing of adiposity rebound and later adiposity, since early adiposity rebound has been suggested as a marker of early high BMI^{36,37} and of accelerated maturation.^{32,36} Two studies showed that BMI value at age 7 presented the same predictive value for later adiposity identification, in comparison to age of adiposity rebound.^{36,37} Therefore, although age at rebound seems to be predictive of later adiposity, it is not clear whether it is independent of childhood BMI, and it is difficult to measure since it requires several BMI measurements.

Adolescence

Adolescence is the second period of life, after infancy, characterized by intense growth.³⁸ Additionally, it is one of the most complex periods in human growth, since in addition to increases in size, marked changes in body composition are also registered, and morphological signs of maturation are visible.^{16,38} Therefore, adolescence may also be critical for the development of obesity, due to changes on the amount and distribution of body fat.^{15,16,39} On one hand, fat cell number is determined by the end of adolescence and reversal of fat cell number is not possible during adulthood.^{39,40} On the other hand, sex-differences in the prepubertal body composition are modest, but the effect of sex hormones acting during pubertal development, such as oestrogen in girls and testosterone in boys, leads to sexual dimorphism in body composition.^{41,42} Females gain higher amounts of fat mass, especially peripherally, but relatively low fat-free mass, while in males there is a substantial acquisition of fat-free mass during this period, but relatively stable fat mass.^{41,42} Females enter puberty earlier and experience a more rapid pubertal transition, and therefore stop to grow at earlier ages, whereas boys have a longer growth period and attain higher final height.⁴² The combination of these changes in the absolute amount of fat and fat-free mass results in increasing percentage of body fat in females and decreasing in males during adolescence, resulting in 25% and 13% of body fat on average in adulthood, respectively for females and males.^{38,41} Sex-differences in body fat distribution are evident in body shape. In females, there is increased peripheral fat accumulation during puberty, especially on the hips and thighs, leading to a gynaecoid shape; in its turn, males have an android body shape, with greater accumulation of central fat, and relatively stable peripheral fat.^{41,42}

The pubertal timing has also been described as a determinant of obesity. In females, several studies have shown that the earlier the age at menarche, the higher the risk of later obesity.^{43,44} A recent review found that from 34 studies addressing the association between age at menarche and adult BMI, the majority (30 out of 34) reported an inverse association.⁴⁵ The meta-analysis of the 10 cohort studies identified in the review showed that girls with early age at menarche (<12 years) had higher adult BMI by 0.34 kg/m² (95% CI 0.33–0.34).⁴⁵ In boys, studies using age at peak height velocity as an indicator of maturation also reported an inverse association between timing of maturation and later adiposity.^{44,46}

Additionally, some studies have shown that pubertal timing is also predictor of body fat distribution, however, evidence is still scarce and inconsistent, probably because the effects of body fat distribution and of total adiposity are difficult to separate. Data from the Amsterdam Growth and Health Study showed that early age at menarche in girls was associated with a trunk-oriented fat distribution pattern, while in boys age at peak height velocity was not.⁴⁷ This sex-difference could be attributed to differences in the indicator of pubertal timing, however, another study in males using

also age at peak height velocity showed an inverse association with central fat mass: early pubertal onset was associated with higher central fat mass.⁴⁶

Although pubertal timing has been recognized as an indicator of later adiposity, reverse causation cannot be ruled out, since some studies have also shown that higher BMI at early childhood was associated with earlier onset of puberty.^{48,49} Therefore, higher adiposity may induce earlier maturation, and pubertal timing may be a mediator between early and later adiposity.

In addition to physiological changes taking place during adolescence, behavioural changes related to dietary, physical and sedentary habits that occur during this period may also increase the risk of obesity.³⁹ Adolescence is marked by psychosocial and cognitive changes with impact on increased autonomy and behavioural change. There is a transition on the focus of the adolescent from the family to the peers,^{50,51} and adolescents progressively feel to be capable of managing themselves on their own, making decisions and solving their own problems.⁵² These transformations may be accompanied by new behaviours acquisition, for instance the initiation of health-related behaviours such as smoking, alcohol consumption, drugs use or sexual behaviours,⁵³ and also changes in food intake and physical activity patterns.^{54,55} During adolescence an increase in sedentary behaviour and a decrease in physical activity is generally observed,⁵⁴ being the decline in physical activity more pronounced in adolescent girls.^{56,57} These changes in physical activity and sedentary patterns during adolescence may have implications for weight gain in youth.⁵⁸ Regarding food intake, changes during adolescence are related to increased adolescents' autonomy over what, when and where they eat,^{59,60} which may lead to more unhealthy food choices. Studies have shown a decrease in breakfast frequency, and an increase in snacking and fast-food consumption during the period of adolescence.^{55,61} Additionally, time trends in adolescents' food consumption have also shown increased frequency of snacking, meals eaten away from home, and consumption of fast food and energy-dense sweetened beverages.⁶² Furthermore, exposure to media seems to also play an important role in adolescents' habits related to the risk of obesity, by promoting more sedentary activities, consumption of unhealthier foods, and conveying unrealistic thinness as the ideal for beauty.⁶³

Changes in food and physical activity and sedentary habits during adolescence have impact not only due to short-term consequences on weight gain, but also long-term effects because these behaviours formed during adolescence tend to track into adulthood.^{64–66}

Tracking of paediatric obesity into adulthood

A growing body of evidence has shown that obesity in paediatric age tends to track into adulthood. Evidence from the Fels Longitudinal study, which prospectively followed 555 participants throughout paediatric age, showed that BMI in childhood and adolescence was predictive of overweight/obesity at age 35 years.^{67,68} Data from the Bogalusa Heart Study also found that BMI in childhood was associated with adult adiposity levels: overweight children were about four times more likely to become overweight adults.⁶⁹ Different studies have also shown that the risk of adult obesity increased with childhood age at BMI measurement.^{67–70} Guo et al.⁶⁸ showed that the probability of obesity at 35 years increased with increasing age of participants with BMI at or above the 95th percentile: probability of adult obesity was lower than 30% for children aged 5 years with BMI at or above the 95th percentile; between 30% and 60% for girls between 5 and 12 years, and for boys between 5 and 18 years, in that percentile; and above 60% for older adolescents. In the Bogalusa Heart Study, the prevalence of obesity in adulthood was 86% in men and 90% women among those who were obese at age 15–17 years, while estimates were 76% and 78%

for those who were obese at 9–11 years.⁶⁹ Whitaker et al.⁷⁰ showed that odds ratio for adult obesity was 1.3 (95% CI 0.6–3.0) for obese children at 1 or 2 years of age, but much stronger (OR = 17.5, 95% CI 7.7–39.5) for obese adolescents at 15–17 years of age.

The evidence provided by these and other more recent studies was summarized in three systematic reviews, which consistently show the tracking of obesity from childhood into adulthood. Serdula et al.,¹³ in a review including studies from 1970 to 1992, found that although correlation between BMI in childhood and adulthood varied considerably, obese children were at least two times more likely to be obese in adulthood, in comparison to nonobese children. Their results also supported a stronger association with adult obesity when obesity was present in older children, compared to younger.¹³ A later review also found that the risk of overweight tracking was higher for youth presenting higher levels of adiposity, and at older ages – risk of adult overweight was stronger for those who were overweight or obese in adolescence than in childhood.¹⁴ Finally, a systematic review and meta-analysis published in 2016 and including fifteen prospective cohort studies showed that the risk of being obese in adulthood was about five times higher for obese children and adolescents, in comparison to children and adolescents who were not obese.⁷¹ Among obese adolescents, 80% were still obese in adulthood.⁷¹

Paediatric obesity and cardiovascular risk factors

Obesity-related risk factors

Obesity is associated with increased risk of various disorders from different systems, such as cardiovascular, endocrine, pulmonary, gastrointestinal, and psychosocial,^{72,73} and also with cause-specific and all-cause mortality.^{74–77} Overweight and obesity were estimated to cause of 3.4 million deaths worldwide in 2010,⁷⁶ and it has been suggested that the increasing trend in obesity may revert progresses in life expectancy.⁷⁸

The association between obesity and cause-specific mortality is stronger for cardiovascular disease and diabetes, in comparison to other diseases.^{74,78} The Prospective Studies Collaboration,⁷⁸ analysing data from 57 prospective studies with almost 900,000 participants, showed that each 5 kg/m² higher BMI was on average associated with about 40% higher vascular mortality (HR = 1.41, 95% CI 1.37–1.45), and 120% higher diabetes mortality (HR = 2.16, 1.89–2.46), while estimates were 10% for neoplastic and 20% for respiratory mortality. Abdullah et al. also showed that the number of years lived with obesity was directly associated with the mortality risk, and was higher for cardiovascular disease-cause than for cancer-cause mortality.⁷⁴

Given the strong association between obesity and cardiovascular-related mortality, and the high prevalence of obesity, as well as the burden of cardiovascular diseases worldwide, the study of the association between obesity and cardiovascular diseases is of great relevance from a public health perspective. Additionally, as the increase in childhood obesity occurred mainly from 1980s onwards, the first generation with high prevalence of obesity since early ages have not reached the life decades of higher incidence of cardiovascular events (the fifth decade of life onwards) yet. Therefore, the magnitude of childhood obesity consequences, in general and specifically on cardiovascular diseases, are not fully understood yet, and there is particular interest on extending evidence on the effects of childhood obesity on early markers of cardiovascular disease.

Cardiovascular events, such as stroke and ischaemic heart disease, are more frequent from the fifth decade of life onwards.^{79,80} Therefore, limited evidence from longitudinal studies is available on the effect of childhood obesity on adult cardiovascular events,

due to the difficult operationalization of studies with such long follow-up periods. The establishment of birth cohorts intending to follow children throughout the paediatric age and during adulthood will provide important insights into this field, but until now most evidence is available for cardiovascular risk factors, rather than cardiovascular events.

The term ‘risk factor’ was first described by William B. Kannel in 1961, in the context of the Framingham Heart Study.⁸¹ According to the Dictionary of Epidemiology,⁸² a risk factor is a characteristic that is known to be associated with increased probability of an outcome, such as a disease, being denominated as a risk marker if it is not necessarily a causal factor. In the Framingham Heart Study, Kannel and colleagues found that elevated serum cholesterol levels, hypertension and electrocardiogram abnormalities increased the risk of heart disease.⁸¹ Since then, research from the Framingham Heart Study and other studies have identified other risk factors, such as diabetes, smoking, physical inactivity, and obesity, and these factors are usually referred as classical or traditional risk factors of cardiovascular disease.^{83,84} Other factors more recently identified include inflammatory markers, abnormal blood coagulation, homocysteine, among many others, and are described as novel cardiovascular risk factors.^{83–85} An extensive list of independent cardiovascular risk factors have already been identified,⁸³ but the predictive ability and clinical implications of the novel risk factors is not so well identified yet, and traditional risk factors seems to explain most part of the cardiovascular diseases incidence and mortality.^{76,84,86} A study from the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration quantified attributable deaths from risk factors worldwide in 2010, and showed that 63% of deaths due to cardiovascular diseases, chronic kidney disease, and diabetes were attributable to the combined effect of four metabolic risk factors: high blood pressure, BMI, glucose and cholesterol.⁸⁷ In Portugal, estimates from GBD for 2013 showed that high systolic blood pressure, dietary factors, and high body-mass index were the leading risk factors of Disability-Adjusted Life Years (DALYs), mainly related to cardiovascular diseases and diabetes.⁸⁸

Childhood obesity has been found to be associated with increased risk of cardiovascular risk factors as early as in preschool aged children.^{89,90} Most studies have addressed the association for obesity at specific ages, consistently showing that higher adiposity at any age is associated with increased risk of cardiovascular risk factors or events. However, most studies have not taken into account the dynamics of adiposity/BMI across the paediatric age, and the effect of different adiposity trajectories during the life course on adult cardiovascular risk profile is not so well understood.

Studies have evaluated the effect of childhood obesity on adult cardiovascular risk factors, but the results are controversial regarding the effect of childhood obesity independently of adult obesity.^{91–97} One study found no evidence for an association between childhood obesity on adult cardiovascular outcomes,⁹¹ but in general other studies have reported direct associations, although suggesting that the effect was mediated by adult obesity.^{94,95} Two other studies found an association of childhood obesity, but they had not taken into account the potential mediation by adult obesity.^{96,97} A systematic review published in 2010 and including 16 studies on the effect of childhood obesity on adult cardiovascular disease risk found that the association observed for childhood obesity was dependent on the tracking of BMI into adulthood, and that there was little evidence for the independent effect of childhood obesity.⁹³ A more recent systematic review including thirty-seven studies which analyzed the ability of childhood BMI to predict obesity-related morbidities in adulthood concluded that childhood BMI was not a good predictor of adult morbidity, because most obesity-related morbidity occurred in adults who were normal weight children.⁹² However, most of the studies included in this review⁹² were from older cohort studies with

relatively low prevalence of obesity in childhood, and therefore it is important to understand if those findings would be replicated in more recent cohorts with higher prevalence of childhood obesity.

The measurement of independent effects of childhood obesity on morbidity is challenging in terms of the statistical analysis, since childhood and adult obesity are strongly correlated. Several studies have addressed this question using standard regression models, adjusting the association for adult BMI or obesity. Nonetheless, this adjustment may introduce over-adjustment biases⁹⁸ and collinearity problems.⁹⁹ This adjustment may also interfere with the interpretation of the results, since the adjusted estimates represent the effect of change in adiposity between measurements, and not only the effect of childhood adiposity adjusted for adult adiposity.¹⁰⁰ Therefore, more sophisticated statistical techniques, such as structural equation models, may be more appropriate to study the effect of childhood obesity on adult outcomes. For example, in models such as path analysis direct and indirect effects can be estimated and results are easily interpretable.^{101,102}

In the studies measuring the association between childhood obesity and adult cardiovascular outcomes, the need of long follow-up periods may determine some limitations, such as limited information on the exposure for the interim periods. The associations estimated for childhood obesity may be confounded by subsequent changes in obesity throughout the paediatric age that are not measured in some studies. Additionally, changes in the grade of adiposity, and the duration of obesity are also not taken into consideration in most of the studies. Therefore, there is growing interest in studying the effect of paediatric obesity on adult outcomes, taking into account the exposure across the life course of the individuals.

Most evidence about the consequences of childhood obesity is based on the study of BMI, and therefore on the effect of total adiposity. However, the methodological challenges discussed here also apply to the study of the effect of body fat distribution. Moreover, there are additional challenges when studying body fat distribution, since it is not clear what is the best indicator of body fat distribution, namely to measure its effect beyond the effect of total adiposity.

Life course approach to the association of obesity with CV risk factors

The recognition that chronic diseases have long latency periods and their origins early in life led to the need of addressing the impact of different exposures acting across different periods of the life span, and of taking into account the timing of the exposures. Therefore, there has been increasing interest on life course frameworks to conceptualize the aetiology of chronic diseases.^{19,103–105} The life course epidemiology is defined as the study of long term effects of biological, behavioural, and psychosocial factors acting at different stages of the life span on health or disease risk.^{18,19} It addresses the influence of factors that operate across the individual's life course, and also across generations, recognizing the importance of time and timing for establishing causality between exposures and outcomes.¹⁰⁴

Different theoretical models in life course epidemiology have been proposed. The critical period model emphasizes the timing of the exposure – an exposure acting at a specific period may have long lasting and irreversible effects on anatomical structure or physiological functioning ('biological programming').^{18,19} However, as discussed earlier in this paper, there may also be sensitive periods, where the effect of an exposure is amplified when taking place at a specific period.^{18,19} These two concepts share the importance of the timing of exposures for the risk of later outcomes. Another main class of life course models is based on the

accumulation of risk, which suggests that effects of exposures accumulate over time.^{18,19} In the accumulation risk models, the timing could also be a key issue, being possible to have developmental periods when exposures have greater impact. Depending on the exposures and outcomes, accumulation of risk may occur through independent, clustered exposures or chains of risk.^{18,19} In the context of non-communicable diseases, the most common model is the risk clustering, where different adverse exposures tend to cluster (for example, health-related behaviours, or adverse exposures related to adverse social circumstances). The chains of risk, where one adverse exposure may lead to another, are also common, and the accumulation of risk may happen in an additive way or with trigger effects, when the final link in the chain has a marked effect on the risk of disease.^{18,19} All of these models are a simplistic representation of the effect of life course exposures and may be difficult to distinguish. Furthermore, the development of chronic diseases likely results from the interplay of critical period and accumulation risk models.^{104,106}

Given the natural history of cardiovascular diseases with long latency periods and the recognition that early life factors are linked to the development of the disease, the use of a life course approach may provide insight into the comprehension of disease aetiology.^{104,106} Additionally, obesity itself is also influenced by factors acting at different stages over the life course.¹⁰⁷ Therefore, the application of a life course framework for the study of the associations between obesity and cardiovascular disease may be of great relevance for understanding the effects of early obesity and its dynamics across the life span on cardiovascular health. Additionally, this approach has contributed to the better understanding of the interaction of factors occurring throughout life and the association with cardiovascular diseases, and also to the development of new methodologies to study how exposure to obesity across paediatric age impacts on cardiovascular disease.

One strategy to summarize the exposure to obesity has been to specifically investigate the effect of obesity duration, usually assessed through the age of obesity onset.^{94,108–113} However, results are conflicting since while some studies found no association,^{109,110,112} others have shown that higher duration of obesity was associated with worst cardiovascular risk profile in adulthood.^{94,108,111,113} One of those studies has additionally found that the increased risk of impaired glucose metabolism for those with higher duration of obesity was partly explained by attained adult adiposity.⁹⁴ Some inconsistent results between studies may be due to differences in the age of participants under evaluation and in the definition of the outcomes. Additionally, the error in the measurement of duration of obesity using the age of its onset may differ between studies, depending on the total length of follow-up and number of measurements across the period under study.

Another study has suggested the use of "obese-years" as a good indicator of obesity-related health risks.¹¹⁴ Abdullah et al.¹¹⁴ showed that the obese-years, which summarizes duration and grade of obesity, was associated with increased diabetes incidence, suggesting that obese-years was a better indicator of the health risks than BMI or duration of obesity alone. However, both approaches, the duration of obesity and the obese-years, only take into account time lived with obesity (BMI at or above 30 kg/m²), and do not consider fluctuations of adiposity within normal BMI ranges. These approaches assume that health risks are associated only to BMI values above a specific threshold, which is not supported by previous evidence.⁷⁷ Therefore, in general the assessment of the dynamics of adiposity has been simplistic, and most studies do not evaluate duration and grade of adiposity. For that reason, new methodologies to assess the exposure to adiposity, including duration and degree of BMI within the whole BMI spectrum, are warranted.

Another interesting approach to address the lifetime risk associated with obesity is the identification of adiposity trajectories over the life course. The study of growth trajectories in paediatric age has been recognized of great relevance for surveillance and for clinical practice, but it is also very useful for aetiology research.¹¹⁵ Studies have applied different methodologies for growth modelling in paediatric age. Some studies have identified individual growth trajectories,^{116–128} through the application of mixed-effects models, where random effects capture individual variation across time. Other studies have applied a group-based statistical method, where subpopulations characterized by distinct developmental trajectories are identified.^{129–153} Only part of these has studied the effect of growth trajectories on cardiovascular risk factors or metabolic outcomes.^{131,133,144,145,148,152} Generally, studies have found that groups experiencing growth trajectories characterized by higher adiposity, and specially with early obesity onset, are associated with the most unfavourable cardiovascular outcomes. Ventura and colleagues¹³¹ showed that girls in the 'upward percentile crossing' trajectory from 5 to 15 years had highest metabolic risk factors at 15 years, while the 'delayed downward percentile crossing' presented similar levels in comparison to the '50th percentile tracking'. In the Raine Study,¹³³ those in increasing trajectories from birth to 14 years presented the highest insulin resistance levels at 14 years, while the outcome in those from declining trajectories was similar to those in the reference trajectory ('Optimal growth'). Data from the Isle of Wight birth cohort also found higher systolic and diastolic blood pressure at 18 years in the delayed overweight trajectory in comparison to the 'normal' trajectory, but still smaller than the values found for the early persistent obesity trajectory.¹⁴⁴ In the EPITeen cohort, from Porto, Portugal, the 'Higher BMI growth' trajectory from birth until 21 years,¹⁴⁵ as well as the 'High, increasing' BMI trajectory identified in the same cohort, but specifically in the period between 13 and 21 years,¹⁴⁸ were associated with the most unfavourable cardiovascular risk profile at 21 years. Data from the Birth to Twenty (Bt20) cohort showed that trajectories of early onset obesity or overweight from 5 to 18 years had higher blood pressure levels in late adolescence.¹⁵² On the other hand, trajectories with a declining trend presented in general levels of cardiovascular risk factors between the trajectories of stable high adiposity or increasing trends, and the normal or optimal growth trajectories.^{131,133,144,148,152} As trajectories with declining adiposity trends approach final adiposity levels of the normal trajectories, these results may suggest that excessive gains in adiposity during the paediatric ages are associated with adverse cardiovascular risk factors, partly because it is likely to result in high final BMI.

Conclusions

This review highlights the relevance of taking into account the exposure to adiposity throughout the life span to better understand the role of adiposity as determinant of morbidity and mortality. However, this life course approach raises methodological challenges that have not yet been fully addressed and solved. Although it is still unclear what the best approach is, the study of the effect of BMI at different ages with adjustment for final attained BMI is recognized to present limitations. On the other hand, methods that take into account variations in adiposity across time, and also across the entire BMI spectrum, may be considered as superior approaches. Nevertheless, further investigation is needed to explore the best methods to summarize the dynamics of adiposity across time.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was funded by FEDER through the Operational Programme Competitiveness and Internationalization and national funding from the Foundation for Science and Technology – FCT (Portuguese Ministry of Science, Technology and Higher Education), under the *Unidade de Investigação em Epidemiologia – Instituto de Saúde Pública da Universidade do Porto* (EPIUnit) (POCI-01-0145-FEDER-006862; Ref. UID/DTP/04750/2013); and the PhD Grant SFRH/BD/78153/2011 (Joana Araújo), co-funded by the FCT and the POPH/FSE Programme.

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