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Lucy R. Green
Robert L. Hester *Editors*

Parental Obesity: Intergenerational Programming and Consequences

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Parental Obesity: Intergenerational Programming and Consequences

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Preface

We fat all creatures else to fat us, and we fat ourselves for maggots. Your fat king and your lean beggar is but variable service, two dishes, but to one table; that's the end.
Hamlet. A tragedy by William Shakespeare (1599/1601).

There is more to our state of adiposity than simply what quality of meal we are offering the maggots upon our demise. Obesity brings with it greater risk of non-communicable diseases such as cardiovascular disease, diabetes, musculoskeletal disorders and cancer. It no longer seems likely that the escalating incidence of obesity and these related diseases can be mitigated by just changing adult lifestyle and diet. Now the concept of a developmental origin of health and disease (DOHaD) is firmly part of scientific, clinical and health policy activities aimed at understanding and reducing the risk of non-communicable diseases. But the focus of the field has moved from small babies and maternal undernutrition to the other end of the nutritional spectrum, maternal obesity and the future life of the larger baby. It seems that obesity begets obesity, and so the cycle continues, as is evident from the more than doubling of the worldwide prevalence of obesity since 1980 [1]. The time is ripe for this book.

The chapters are authored by undisputed leading scientists, clinicians and policy makers in this field. In these chapters, the authors set out their ideas and provide an up-to-date synthesis of the current thinking about the problem of parental obesity, the ideas of intergenerational programming, and the physiology behind it. We hope that this book will therefore appeal to a broad readership of students, clinicians, researchers and health policy makers who either seek an introduction to the area of DOHaD or have a specific interest in the pathogenesis of obesity.

In this book, the spotlight is on critical periods in development when obesity might affect offspring physiology, sometimes even before a mother conceives or is aware that she is pregnant. These effects appear to have a legacy across several generations. In Chap. 2, Gaillard and Jaddoe draw upon their considerable experience and data from the observational Generation R study, and in Chap. 3 Patel and Poston write from the perspective of their

recent randomized control trial (RCT) of a diet and physical activity intervention (UPBEAT). In both chapters, the authors call for more RCTs to understand intergenerational programming. The impact of maternal obesity on offspring physiology is multifaceted and linked to disease of the cardiovascular system and metabolism, to allergic diseases (see Chap. 15) and to cancer (Chap. 13). The importance of early critical windows is emphasized by research (Chap. 5) showing the potential for the environment around time of fertilization (pre-implantation) to have a lasting impact on offspring physiology. Indeed many contributors to this book recommend that in order to break the 'intergenerational cycle' of obesity, interventions should target obesity in the preconception period as well as throughout pregnancy. Nevertheless, others argue for a better evidence base, since there may be negative implications of dietary restriction/weight loss or exercise before or around time of conception (Chap. 7). Part of this evidence base is likely to concern the 16 million women 15–19 years old who give birth each year, about 11 % of all births worldwide [2]. The way in which weight gain and obesity during pregnancy in the young, still-growing mother affects offspring is more complex (Chap. 4) and the use of the sheep as a model for this has produced important mechanistic insights.

"Women are responsible not only for the health of their own offspring but also for the cost to the community of an unhealthy future population. . . . Women are caught in a pincer movement between those seeking to protect the fetus and those concerned with the social and economic cost or burden of ill health" wrote Ray Noble (2006) [3]. Therefore, it is timely that research into the influence of paternal obesity on offspring physiology has burgeoned (Chap. 6). Obese fathers are more likely to father an obese child with impaired glucose metabolism, an effect which may then extend into the next generation. These observations have the potential to shift at least some of the burden of responsibility for lifestyle intervention pre-pregnancy from the mother to the father.

To understand causality in human observational studies of maternal obesity and impact on offspring, more sophisticated study designs and detailed maternal-offspring outcome measurements are now needed (Chaps. 2 and 3). However, over the course of this book the reader will discover that substantial advances in understanding the mechanisms and pathways linking parental obesity to offspring physiology are being made using animal models. As with drugs, overeating may involve a chronic cycle of intoxication ('positive reinforcement') and the emergence of withdrawal anxiety over time that perpetuates disordered eating. The physiological evidence described in Chaps. 9 and 10 that pregnancy high fat diet/obesity alters both maternal behaviour towards her offspring and leads to altered food preferences in them, along with heightened risk of mental ill-health, increased anxiety, social behavioural deficits and impaired memory and learning is of real concern.

Current knowledge is expanding on the mechanistic basis of the imbalance between appetite and satiety, and of adipogenesis-lipogenesis in the offspring of mothers with high fat intake during pregnancy (Chap. 11). Leptin, an adipokine peptide hormone produced by fat cells, can cross the blood-brain barrier and in offspring of maternal obesity/high fat pregnancies its action in the hypothalamus is implicated not only in the dysfunction in appetite/satiety pathways (Chap. 11), but also in cardiovascular dysregulation and hypertension (Chap. 14). Furthermore, the mechanisms underlying insulin resistance in offspring of high fat fed and obese mothers are likely to involve changes in insulin sensitivity in skeletal muscle and liver (Chaps. 7 and 8). Nonalcoholic fatty liver disease (NAFLD), whereby fat accumulates in the liver, is the hepatic manifestation of the metabolic syndrome. There is now considerable evidence to suggest that NAFLD in offspring is primed by high fat diet and obesity during pregnancy (Chap. 12). The disease can progress in severity and lead to the development of fibrosis and cirrhosis, and may be linked to hepatocellular carcinoma. The increased risk of malignancy in offspring of obese pregnancies is an emerging field of research and the most persuasive evidence to date is from rodent studies in which the incidence of mammary tumours in female offspring is heightened (Chap. 13).

Throughout the book, and summarized in Chap. 16, contributors highlight epigenetic mechanisms that may help to explain the intergenerational cycle of obesity and physiological dysregulation. It is clear that the advances in the knowledge of epigenetic mechanisms have brought 'environmental sense' to the world of genomics. In addition, the microbiome has provided a new mechanistic perspective on the intergenerational programming of obesity and physiology. Evidence of the susceptibility of the early life microbiome to programming by maternal diet, antibiotic exposure, mode of delivery and breastmilk offers an exciting avenue for understanding how the changes in the early life environment (such as maternal obesity and weight gain) influence the health of the next generation and possible future interventions (Chap. 17).

The importance of parental obesity as a major risk factor for non-communicable diseases is apparent from the outset of this book. The reader gets a sense of the urgency for action if adolescents and young adults are to have a better future, the cost associated with non-communicable diseases is to be reduced, and if the intergenerational programming of obesity is to be halted (Chap. 1). Many of the contributors to this book have synthesized the current state of research into the mechanisms linking parental obesity to altered offspring physiology, and suggest targets for future interventions. Realizing the potential of such interventions is important but enormously challenging and, as the reader will appreciate from Chap. 1, this must be done within a coordinated policy scheme at international, national and local government level.

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Contents

Chapter 1
Why Obesity in Parents Matters

Mark Hanson

Abstract Promoting the best possible environment for early human development offers one of the greatest missed opportunities today for improving global health, human productivity and longevity. Overweight and obesity in parents and parents-to-be are not only associated with poorer health prospects for this section of the population in the future, but also pass the risk of overweight and obesity to their children. This calls for a new initiative to improve the health of current and prospective parents, commencing with adolescent girls and women of reproductive age, but also their partners.

Keywords Obesity • Parents • Generations • Public health • Education • Childhood • Diabetes • Cardiovascular

1.1 The Challenge

Non-communicable diseases (NCDs), including diabetes, cardiovascular and lung disease, some forms of cancer, mental illness, musculoskeletal disorders and some atopic and allergic conditions now account for almost two-thirds of deaths worldwide and a substantial burden of morbidity. WHO figures show that 38 million people die from NCDs each year, 28 million of these deaths occurring in low-middle income countries [1]. NCDs incur enormous costs in health care, which are challenging even in high-income countries. For example, the McKinsey Global Institute estimates that reversing the rising prevalence of the major NCD risk factor obesity in the UK could save the NHS $1.2 billion/year [2]. The scale of the economic costs is unsustainable, especially in low-middle income countries. NCDs not only cause deaths and shorten lifespan but they can also impair neurocognitive development [3, 4] reducing productivity and well-being. Hence,

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apart from direct health-care costs, there will be significant economic benefits from reducing the burden of NCDs in all countries.

Until recently, it was widely believed that risk of NCDs in individuals was a combination of fixed inherited genetic risk factors and an unhealthy lifestyle in adulthood. However, genome-wide association studies have not found genetic variants which account for a substantial fraction of risk at the population level (e.g. [5]), and whilst overweight and obesity were estimated to produce 3.8 m deaths globally in 2010, there are as yet no successful national campaigns for tackling the problem [6]. The challenge is to find a new approach.

Overweight and obesity are important and very widely known risk factors for NCDs [1] and so emphasis on preventing them makes much sense. The problem is often thought to commence in childhood, as obesity in children has long-term effects on a wide range of organ systems [7]. The problem of childhood obesity in both high and low-middle income countries led to the establishment in 2014 of a Commission on Ending Childhood Obesity by Dr Margaret Chan, the Director-General of the World Health Organization [8], which will report in early 2016. Obese children have long been known to be more likely to become obese adults [9], and globally, 1.9 billion adults aged 18 years and older were overweight or obese in 2014 [10].

Turning to parental effects, in England in 2013 for example, 48 % of women of reproductive age were overweight or obese [11]. Being overweight or obese will affect their health and increase the risk of complications during pregnancy and delivery [12]. Even more important is the fact that obese women tend to have obese children and maternal obesity is a major factor in the preconceptional and fetal or infant origins of later risk of NCDs in the offspring [13]. This volume attests to the considerable concern about the effects of obesity in parents on their children, especially in mothers, but there is increasing evidence for an increased risk of obesity in children with two obese parents [14, 15] and there is accumulating experimental evidence for a role of paternal effects in transmission across generations [16].

Meeting the challenge posed by obesity in parents also has important social and equity implications, because it is particularly of concern in women with low educational attainment or socio-economic status [17], and in some ethnic and migrant groups [17, 18]. Obesity and the resulting increased risk of NCDs can perpetuate or even widen social inequalities in health [19] adding another level of urgency to finding a new solution to the problem.

The major focus of this chapter is on the biological rather than the social processes by which parental obesity affects the next generation. The distinction between the two is somewhat artificial and should not be taken to imply that aspects of parental behaviour, the family environment, etc., do not play a role in inducing obesity in children and adolescents, or are not areas where potential interventions could have major effects (see for example [20]). There have been some very hopeful initiatives in this respect such as the Family–Nurse Partnership [21] and the Abecedarian project [22] in which wider social considerations about family life and child education have been shown to improve long-term health outcomes including obesity.

1.2 New Insights into the Importance of Healthy Early Development

New research in the field of developmental origins of health and disease (DOHaD) has focused attention on the processes of developmental plasticity, operating during critical periods of early human life to affect growth and development of tissues, organs and physiological control systems [13, 23]. The critical periods of development commence in the early embryo [24], sometimes before the woman knows that she has conceived, and continue through pregnancy [25, 26], infancy and childhood and into adolescence [27]. During these periods the developing individual responds to aspects of their environment, via the mother and placenta before birth, and via breast milk and parental behaviours after birth. Signals relating to maternal nutrition, body composition, physical activity, stress, behaviour and exposure to chemicals and toxins can set the level of the developing individual's responses to later challenges such as living in today's highly obesogenic, increasingly urban, environment [28]. In this way, the effects of unhealthy lifestyle are passed from one generation to the next and can be amplified. This amplification is greater when there is a mismatch between the developmental and adult environments, as happens for example with nutritional and other lifestyle transitions in countries undergoing socio-economic transitions and in migrant groups [29]. These new concepts are fundamental to understanding the growing challenge of NCDs worldwide. They also offer opportunities for promoting future health for the current and future generations at several points in the human reproductive cycle (Fig. 1.1). However, once a critical period has passed intervention is much more difficult, becoming less effective and potentially more expensive. This is one of the reasons why current approaches to reducing the incidence of NCDs in adults may not be achieving the results needed. One of the most important phases in which to prevent and reduce overweight and obesity is during adolescence and the reproductive years, as this will not only promote the health of the woman but also that of her child(ren).

1.3 Obesity in Adolescents and Young People

Apart from the longer-term effects of obesity in increasing the risk of NCDs referred to above, there are a range of short- to medium-term implications which apply specifically to women of reproductive age and to a lesser extent to their partners. These are perhaps not sufficiently emphasised as they could help increase motivation to adopt healthier behaviours. Obesity in women is associated with reduced fertility rates and greater risk of early miscarriage [30] and to reduced sperm counts and morphological abnormalities [31]. The early embryos of obese mothers already show signs of abnormal development and metabolism [32]. Obesity in pregnancy is associated with increased risk of gestational diabetes [33] which, if poorly controlled, can result in the perinatal complications of fetal

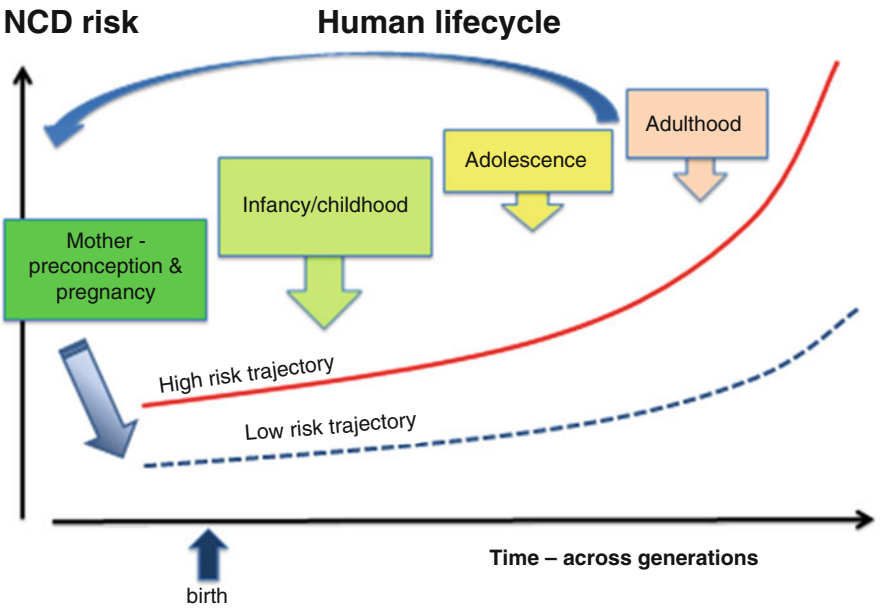

Fig. 1.1 Life-course view of NCD risk. Risk of NCDs increases in a non-linear way throughout life, starting before birth. The trajectory of risk can be affected by interventions at various times, although establishment of a low-risk trajectory must be early in the life course, especially preconception and in pregnancy (broad *blue arrow* on *left*). Risk reduction in adolescents or young adults can not only affect their later health but, as they are future parents, reduce inherited risk in their children (human life cycle *arrow*)

macrosomia, shoulder dystocia, obstructed labour and neonatal hyperinsulinaemic hypoglyceamia [34]. The specific role of pre-pregnancy weight and weight gain in pregnancy in these conditions [35], related to ethnicity [36], may offer new avenues for intervention. Maternal hyperglycaemia is also associated with higher incidence of a range of congenital abnormalities in the baby [37].

It is estimated that there are 1.8 billion people aged 10–24 years in the world today, comprising about one-quarter of the total global population. In some countries, especially in sub-Saharan Africa, they represent an even higher proportion of the population. Adolescence is a time in life when many behaviour patterns become established and is a time when interventions might reverse the effects of earlier poor development [38]. Many adolescent people are overweight or obese (e.g. for England see [39]) and have markers of cardiovascular risk, including elevated blood pressure and lipid or insulin/glucose levels [40]. A high proportion of adolescents and young women and men have an unhealthy lifestyle, with poor diet, low levels of physical activity, smoking, excessive alcohol consumption and use of recreational drugs [41–43]. These lifestyles will have adverse later health implications for the individuals, but will also have repercussions on the development and health of their future unborn children, giving the next generation a poor start to life. Access to health care is fragmentary in this section of the population,

even in high-income countries. Adolescents frequently defer, or discount, any action to improve their health until the future [44, 45] and for those adults with lower educational attainment and socio-economic status poor health can become self-fulfilling prophecy [46].

For those women who become pregnant, contact with health-care services often does not occur until late in the first trimester, by which time the pregnancy is well established and it is too late for modification of risk factors which affect embryonic development. In most high-income countries, prospective parents do not prepare for pregnancy [47]; this is even more true of many low-middle income countries. In the UK, however, it is suggested that more than two-thirds of pregnancies are in fact planned to some degree, at least in the sense that contraception has not been routinely used [48].

1.4 Meeting the Challenge

Most societies do not have in place coordinated schemes to promote the health of adolescents and young people, in particular before conception [49], as this is assumed to be part of routine public health primary care, which is not always the case [50]. This is an important missed opportunity to prepare for pregnancy, to promote healthy pregnancy and to ensure healthy outcomes [51, 52].

Formal educational programmes delivered through schools have only had small effects on, for example, levels of obesity and risky behaviours, and it appears that integration of such programmes more widely into the community and involving parents will improve success [53–55]. New integrated pedagogical approaches are necessary to promote health literacy, for example through linking schools and health researchers through out-of-classroom activities which incorporate continuing professional development for science teachers, hands-on exposure to research methods and ‘meet the scientist’ encounters for school age students [56].

There are three interrelated policy implications in addressing the challenge of parental obesity, which need to be considered simultaneously, both in terms of their implementation and their assessment (Fig. 1.2). While concern about the impact of parental obesity is a global issue, these components will have to be implemented at the level of national and local governments, in order to make them culturally specific. They are:

(a) *Profile and priority*. Make the health of adolescents and young women and their partners a national priority, on a par with events and movements which promote an image of vital, active collective life, e.g. the Olympic Games. This requires establishment of national organisations with professional representation from health, education, communities and local governments, media, sport and the private sector.
(b) *Create demand* by investing in health literacy promotion through education programmes in schools linked to community-based initiatives involving a range

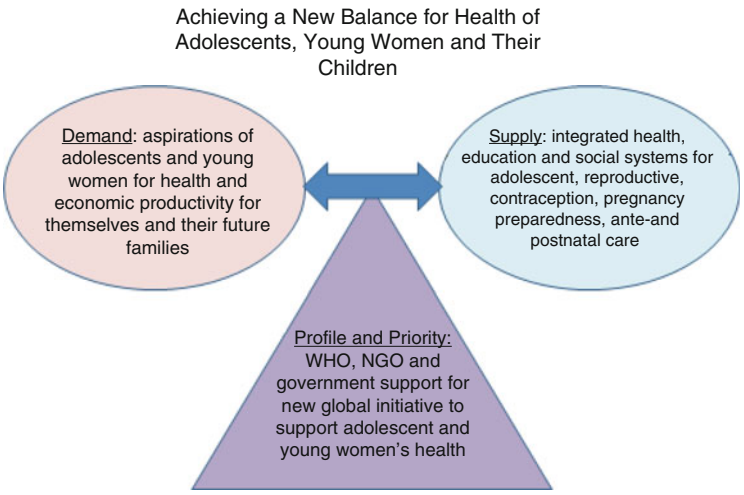

Fig. 1.2 Achieving a new balance for health of adolescents, young women and their children. Promoting health at this time in the life course requires a balance between the supply of health, education and social care services and the demand for such provision based on appreciation of their importance for health and prosperity. This balance needs to be supported through the profile and priority given to it by a range of government and other organisations

of organisations and sponsors. This investment is predicated on the projected return through reduced health care and other costs of reducing parental and childhood obesity, adverse pregnancy outcomes and early markers of NCD risk.

(c) *Supply*. Establish integrated systems for the provision of health care to adolescents and women before conception, throughout pregnancy and delivery and after birth, linked to family planning and sexual health services, primary care and wider community organisations.

1.5 Conclusion

The challenge posed by parental obesity, and obesity in parents-to-be, requires urgent action, because such obesity does not augur well for the health of these adolescents and young adults in the future. As this section of the population have a substantial proportion of their lives ahead of them, the costs of NCDs in terms of their well-being, productivity and longevity as well as the direct health-care costs will be very hard to meet, even in high-income countries. Worse, such ill health passes the risk of overweight and obesity to their children by a range of mechanisms. There is a need to establish a new approach to meeting this challenge, in terms of raising the profile and priority accorded to the issue at the level of national and local governments and in conjunction with organisations such as WHO; creating awareness of the problem and a desire to address it among young people, especially adolescents; and providing an integrated health-care delivery system

linked to education and wider community initiatives to ensure that parents do not miss the opportunity for health promotion at a time in their lives which is critical for them and their children.

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