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EDITORIAL

# A life course perspective on diabetes: developmental origins and beyond

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We are all very well acquainted with the enormous and increasing impact of diabetes mellitus on individuals and society worldwide. The World Health Organization estimates that the number of people with diabetes worldwide rose from 108 million in 1980 to 422 million in 2014 [1]. The global prevalence in those aged more than 18 years increased from 4.7% to 8.5% over the same period. The prevalence has increased more rapidly in middle- and low-income countries and in those who are socially deprived.

Type 2 diabetes, once considered a disease of old age, sadly now occurs not uncommonly in children and young adults. Diabetes thus affects everyone, from cradle to grave. Indeed, there is strong evidence that exposure to the diabetic milieu in utero has intergenerational, long-lasting effects on the offspring of the index pregnancy and perhaps even on their offspring. The rising prevalence seems mainly due to changing lifestyle, with increasing energy intake and less energy expenditure, although other potential drivers should not be forgotten.

Delay in onset, if not prevention, of a large proportion of cases should be possible. However, although individual 'diabetes prevention programmes' have generally been successful in research settings, translation to routine use has had less impact. Government bodies have also been slow to develop effective prevention programmes to help high-risk individuals and to take population-based initiatives.

For all these reasons, *Diabetologia* has chosen 'A life course perspective on diabetes: developmental origins and beyond' as our 2019 special edition. We have been fortunate to receive contributions from world-leading experts, tackling a wide range of relevant topics. The issue covers evolution and the diabesity epidemic, sex differences in type 2 diabetes and cardiovascular disease burden, under- and overnutrition and obesity/diabetes risk, maternal and paternal in utero programming, environmental agents as diabetes risk factors, the impact of early-life factors on type 1 diabetes, and cellular senescence and ageing effects in diabetes. We conclude with a piece tackling the question: what should governments do?

Susceptibility to diabetes differs markedly within and between human populations. Going beyond conventional physiological explanations, Jonathan Wells [2] begins our special edition by offering an evolutionary perspective on the source of metabolic variability associated with diabetes risk. The approach builds on a simple 'capacity–load' model of disease risk that can be explored by assessing components of body composition at different stages of the life course. On the one hand, stable ecological stresses that characterise particular geographical regions may have shaped population variability in metabolic traits, resulting in differential risk of diabetes across ethnic groups in contemporary environments. On the other hand, developmental responses that have evolved under selective pressure to maximise reproductive fitness rather than health may contribute to individual variability in diabetes risk, depending on the stimuli and stresses encountered through the life course. Wells states that, collectively, this evolutionary perspective sheds new light on variability in diabetes risk and highlights new opportunities for interventions.

Huebschmann et al [3] then go on to specifically highlight the underexplored sex and gender differences in the prevalence of type 2 diabetes and cardiovascular disease across the lifespan. Population-based studies reveal greater insulin resistance and prevalence of youth-onset type 2 diabetes in girls in most studies, whereas both insulin resistance and diabetes prevalence demonstrate a modest male preponderance in adults. However, these patterns are not observed in all countries, suggesting regional variation in genetic and environmental mediators. The authors state that the absolute risk of cardiovascular disease in women with diabetes is similar to that in men with diabetes. However, the presence of type 2 diabetes confers a 25–50% increase in the relative risk for cardiovascular disease in women as compared with men. They suggest that

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further studies need to unravel the drivers of sex differences in diabetes prevalence across the lifespan and the mediators of the accelerated risk of cardiovascular disease in women with type 2 diabetes, to inform effective sex-specific interventions for the prevention of diabetes and its complications.

As mentioned previously, type 2 diabetes was traditionally considered to be a disease with origins in adulthood. Stein and colleagues [4] show how this idea was challenged by research evidencing an inverse association between birthweight and risk of type 2 diabetes, suggesting that fetal undernutrition was contributory (a counterintuitive idea). Follow up of people who were exposed to intrauterine 'famine' has supported the idea that fetal undernutrition predisposes to future risk of non-communicable disease. Birth cohort studies in low- and middle-income countries have expanded this idea to highlight the role of maternal undernutrition (particularly in relation to micronutrients), as well as overnutrition (maternal obesity and gestational diabetes), in increasing the risk of offspring adiposity, diabetes and other non-communicable diseases. The authors highlight that studies in India and Central America have provided promising data supporting the use of nutrient-rich supplements in women before pregnancy and in children to help increase offspring birthweight and reduce diabetes risk in later life, respectively. They state that there is a need to support further public health programmes aimed at intergenerational (primordial) prevention of non-communicable disease, including diabetes.

In contrast, Perng and colleagues [5] discuss how developmental overnutrition, resulting from maternal diabetes, obesity, maternal dietary intake during pregnancy, excess gestational weight gain and infant feeding practices, may play a role in obesity and type 2 diabetes in childhood. Childhood obesity has reached pandemic proportions and youth-onset type 2 diabetes is following suit. The review by Perng et al provides a critical summary of current evidence and discusses shared and distinct underlying pathways associated with the link between developmental overnutrition and childhood obesity/type 2 diabetes. The authors draw on this information to make suggestions for meaningful aetiological, clinical and public health research that may ultimately break the intergenerational cycle of obesity and diabetes.

Fernandez-Twinn and colleagues [6] summarise recent evidence for a role of the in utero environment in contributing to the risk of obesity and type 2 diabetes in later life. Both observational human studies and animal functional studies are discussed, including emerging evidence of potential molecular mediators of in utero 'programming', such as epigenetic variation established in early development. It is clear that a complex interplay exists between a range of environmental exposures, nutritional status and genetic variation in establishing metabolic risk of offspring. The authors suggest that further longitudinal human studies, complemented by direct animal experiments, are needed to identify potential preventative strategies and interventions to modify the trajectory of metabolic risk from very early life.

The review by Sharp and Lawlor [7] reminds us that research on the early life origins of health and disease has traditionally focused on maternal (mostly intrauterine) impacts on offspring health; however, there are now increasing calls for more research on paternal influences. The authors discuss the public health, policy, social and clinical implications of a better appreciation of the idea that fathers can influence offspring risk of obesity and type 2 diabetes. They also summarise potential mechanisms through which paternal impacts on offspring health might occur and provide a systematically compiled overview of the current evidence linking paternal factors to offspring development of obesity and type 2 diabetes throughout the life course. Finally, the authors discuss future challenges of research in this area and suggest potential strategies to overcome them.

Burgeoning evidence from cell-based, animal and epidemiological studies now implicates exposure to endocrine-disrupting chemicals in the pathogenesis of type 2 diabetes. In their review, Sargis and Simmons [8] outline the evidence linking endocrine-disrupting chemicals to defects in glucose homeostasis, using bisphenol A as an example. They focus specifically on mechanisms of metabolic toxicity and sensitive developmental periods during which toxicant exposures are particularly deleterious to long-term and multigenerational metabolic health. Finally, evidence is presented implicating the disproportionate exposure to environmental toxicants among vulnerable communities in the genesis of diabetes disparities. The authors state that, together, these data raise the spectre that endocrine-disrupting chemicals are under-/unappreciated disease risk factors that have been neglected by the diabetes care community until now. Moving forward, they suggest that improved knowledge of the contribution environmental toxicants make to the global burden of diabetes will offer novel clinical and policy avenues for reducing the global burden of disease.

Much of the above work has concentrated on type 2 diabetes. However, over recent decades, birth cohort studies, clinical trials and epidemiological studies have enhanced our understanding of how environmental exposures during pregnancy and early life contribute to type 1 diabetes risk. Craig et al [9] detail how the virome, microbiome, dietary factors and weight/insulin resistance may interact with the human genome and metagenome at multiple timepoints during early life to initiate the development of islet autoimmunity and progression to type 1 diabetes. They state that the current era of 'omics' has the potential to deliver new insights into the complex interplay between genetic predisposition and environmental determinants in the pathogenesis of type 1 diabetes.

With the impact of early-life exposures on diabetes risk being extensively discussed, Palmer and colleagues [10] go

on to describe how ageing can impact type 2 diabetes risk. Ageing is a major risk factor for the development of type 2 diabetes, and hallmarks of ageing are also present in multiple tissues of individuals with diabetes. In their review, Palmer et al discuss the role that fundamental ageing mechanisms, in particular cellular senescence, play in driving the changes seen in diabetes. The authors summarise the current data on cellular senescence in key target tissues associated with the development and clinical phenotypes of type 2 diabetes. They highlight the therapeutic potential of senolytics, which selectively target senescent cells and are currently being investigated in clinical trials for other conditions. The authors suggest that senolytic therapeutics hold promise in the treatment of diabetes and its complications.

Our final contribution, by Timpel and colleagues [11], tackles perhaps the most pressing question of all: what can (and indeed should) governments do to prevent diabetes through the life course? Health systems and governments are increasingly required to implement measures that target at-risk populations to prevent noncommunicable diseases. In their review, Timpel et al highlight what governments should be doing to prevent diabetes throughout the life course, targeting: (1) pregnant women and young families; (2) children and adolescents; (3) the working-age population; and (4) the elderly. They state that the evidence to date supports the effectiveness of some known government policy measures, and that many of these appear to be more effective if they are part of a bundle of strategies and if they are supplemented by communication strategies. They go on to suggest that, although there is a current focus on strategies that target the individual, governments can make use of evidence-based, population-level prevention strategies. The authors conclude that more research is required, including continuous evaluation of the overall and subgroup-specific effectiveness of policy strategies.

Halting and reversing the epidemic of diabetes and obesity requires the knowledge, skills and expertise of many individuals from a wide range of disciplines, including clinicians, basic scientists, epidemiologists, public health experts and psychologists, to name but a few. We hope that everyone, regardless of their background, is inspired by some aspect of this special edition of *Diabetologia* to intensify their efforts towards diabetes prevention.

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