**The Inheritance of Cardiovascular Disease Risk**

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Abstract

Cardiovascular disease (CVD) is foremost among the non-communicable diseases (NCDs) which account for 71% of deaths globally each year. CVD is also prominent among the pre-existing conditions still accounting for nearly 25% of maternal deaths, and is linked to gestational diabetes and preeclampsia. Markers of CVD risk have been reported even in young children, related to prenatal factors such as mother’s diet or body composition. The underlying mechanisms include epigenetic changes which can alter the trajectory of risk across the life course. Preventive interventions need to commence before conception, to reduce transmission of CVD risk by promoting healthy behaviours in prospective parents, as well as in pregnancy, and postpartum through breastfeeding and healthy complementary feeding. Surprisingly, these opportunities are not emphasised in the 2018 United Nations Political Declaration on NCDs. NCDs such as CVD have communicable risk components transmitted across generations by socio-economic as well as biological factors, although the former can also become embodied in the offspring by epigenetic mechanisms. The inheritance of CVD risk, and social inequalities in such risk, thus raise wider questions about responsibility for the health of future generations at societal as well as individual levels.

Key words: cardiovascular; inheritance; transgeneration; epigenetic; DOHaD

Abbreviations:

BMI – body mass index

CpG – cytosine-guanine dinucleotide

CVD - cardiovascular disease

DOHaD – developmental origins of health and disease

EU – European Union

LMIC – low-middle income country

NCD - non-communicable disease

SDG - Sustainable Development Goal

SNP – single nucleotide polymorphism

Key Notes

* Cardiovascular disease (CVD) is foremost among the non-communicable diseases (NCDs) which account for 71% of deaths globally each year.
* CVD has communicable risk components transmitted across generations by socio-economic as well as biological factors, which can also become embodied in the offspring by epigenetic mechanisms.
* The inheritance of CVD risk raises questions about responsibility for the health of future generations at societal as well as individual levels.

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Introduction – a global problem

Non-communicable diseases (NCDs) now account for 71% of all global deaths each year and so demand urgent action (1). The NCDs include cardiovascular diseases (CVD), diabetes, chronic lung disease and some forms of cancer. CVD is the leading NCD (2), accounting for nearly one third of all deaths (3) and a substantial burden of life years lost (4). This burden of disease is recognised to be greater than that from communicable diseases (5). On the positive side, there has been a reduction in CVD risk factors in recent years, due on the one hand to reductions in behavioural factors such as smoking, poor diet and sedentary lifestyle, and on the other to improved risk reduction therapies such as statins, niacin and fibrates (6). However on the negative side this reduction is largely in high income countries (7) and the impact of CVD is likely to be more apparent in low-middle income countries (LMICs) as the burden of infectious diseases falls (5). Further, the risk factor of obesity is reaching epidemic proportions, and if unchecked by 2025, global obesity prevalence is predicted to reach 18% in men and over 21% in women (8). There is no sign of this risk declining. The economic consequences of this problem are substantial and are likely to have serious long-term effects, especially for LMICs as their economies grow following reductions in communicable diseases.

Given the scale of this challenge, it is remarkable that it took so many years to be recognised. NCDs did not figure in the Millennium Development Goals at all and it was not until 2011 that the first United Nations High Level Meeting on the prevention and control of NCDs took place (9). This was a visionary document, which set out clear recommendations for action across many domains, from healthcare through civil society to engagement with the private sector. It established the basis for the inclusion of reduction in NCDs in the Sustainable Development Goals (SDGs), especially SDG 3.4 (10). Two United Nations High Level Meetings have taken place since 2011. However the report of the third High Level Meeting, in 2018 (11) emphasised that progress towards meeting SDG 3.4 has not been sufficient. The recent report on the Global Burden of Disease Study (12) states that no countries are projected to meet the target reduction in deaths from NCDs by 2030 – the date set for attaining the SDGs.

Whilst there have been improvements in early diagnostic measures for CVD, their use is relevant to high resource settings and is not without problems (e.g. see 13,14) and newer therapies for risk reduction as noted above (6), the reduction of such risk overall on a global scale does not seem to be taking place. This is particularly true of obesity. Weight loss in adults is notoriously hard to achieve and maintain, in part because it is very hard to reset appetite and satiety mechanisms to a new level even after a prolonged period of enforced weight reduction (15). Apart from the plethora of amateur, professional and proprietary weight loss products and manuals, the nutritional literature reports a range of views about the roles weight loss or health promotion of low-fat versus low-carbohydrate diets (16), dietary fibre (17) and polyunsaturated fatty acids (18) and their interaction with statins (19).

Not surprisingly, members of the public are confused by these apparently conflicting professional opinions and consequently disinclined to act. This lack of motivation is diametrically opposed to the view of many Western governments which seek to transfer responsibility to individuals, to avoid a “nanny state” policy. This is sometimes justified in neo-liberal political terms, but in reality it places the responsibility for action on precisely those individuals least able to do so, especially those of low educational attainment or socio-economic status, rather than recognising the wider social contexts which lead to unhealthy lifestyles (20). A particular problem in relation to nutrition is that a high percentage of the foods consumed globally are produced by a relatively small number of multinational companies. As these operate across national jurisdictions, they cannot easily be regulated by nation states through legislation, taxation etc. Whilst some countries have imposed taxes on, for example, the sugar content in beverages, such measures alone are unlikely to have substantial impact.

In summary, it seems that for CVD, i.e. NCD, risk factors in particular obesity, we face a perfect storm (21). The evidence on how best to reduce them is conflicting or uncertain; the risks at the population level of not reducing them are large; actors other than national governments play a substantial role with major economic consequences; the need for action to reduce risks has only recently received emphasis at the level of global bodies such as the United Nations; national governments are uncertain about how to act to produce beneficial health effects in the short- to medium-term necessary to derive policy decisions and are unsure of the economic cost versus benefit; the public in many countries are not motivated to act and are confused by conflicting advice, and groups at particular risk are not aware of or engaged with the need to act to reduce such risk. This constitutes a ‘post-normal’ scientific and strategy problem (22). We do indeed have a problem.

Taking a Life Course perspective

From the summary above it is clear that there are important elements of our strategy to address CVD risk factors which are missing. This necessitates taking a new perspective on the problem.

First, even though it is well known that CVDs are chronic conditions, the importance of adapting a life course perspective is not widely appreciated. The life course view of NCDs is that risk commences many years before clinical presentation with disease and can follow several pathways from a theoretical point of view (23,24). Risk is therefore pathway-dependent, i.e. individual risk at any time is not only (or even primarily) dependent on the conditions such as behaviour or environmental exposures at that point in time, but on the pathway across the foregoing life course which an individual took to reach that point. This approach has been particularly applied to ageing, separating health into various domains in which cardio-metabolic function relates to the ability to be mobile, and viewing health as a combination of intrinsic capacity (defined as the composite of all the physical and mental capacities that an individual can draw on) and functional ability (defined as the health-related attributes that enable people to be and to do what they what they have reason to value) (25). This model has applied to cardiovascular function in relation to endothelial function, the effects of oxidative stress, nutrition and stem cell capacities (26).

The extent to which governments in the EU region have adopted a life course approach and developed some policy considerations for implementing and measuring this approach in public health was recently reviewed (27). At the simplest level, there are three phases of the life course relevant to any organ system or functional domain, each of which have consequences for initiatives aimed at reducing risk. The first is a developmental phase, when structure and function increase to a maximum level. The time in the life course when this is achieved varies between the body’s systems: for example for renal function the lifelong complement of nephrons is established prenatally in the human (28) and cannot be modified subsequently; for bone density the maximum is not achieved until late adolescence (29). Notwithstanding this variation, however, the principle holds for all body systems that promotion of healthy development during a critical or sensitive period maximises the peak function attained by an individual.

The second life course phase constitutes a period over which maximum function of the system is maintained (see 30). This is usually several years but may extend to decades. It is important to recognise that here the combination of intrinsic capacity and functional ability, i.e. all aspects of the system, is what matters. Thus, even though the complement of fast- versus slow- twitch skeletal muscle fibres or cardio-myocytes is established in early life, at least in large animals (31,32), the maintenance of maximum skeletal or cardiac muscle function through appropriate levels and types of physical activity can nonetheless involve changes in function across the spectrum of sub-types of skeletal muscle fibres or in cardio-myocyte size and contractility.

The third phase of the life course involves declining function. The rate of such decline can be increased by unhealthy behaviours such as diet or low levels of physical activity, and by infections or accidents such as a fall. There are thus opportunities to slow this rate of decline in individuals by appropriate support and interventions.

One of the essential components of such thinking is that health, for example of the cardiovascular system, is manifest not just as a static level of function, but rather as a response to a challenge. This is also termed resilience, and is represented by the slope of the curve of risk across the life course in Figure 1. Clinically, this is widely understood, even if not formally recognised. For example it is clear that the level of basal blood pressure or heart rate are less useful than a measure of the cardiovascular response to an exercise test. This is important because in fact aspects of cardiovascular function and resilience are easily measured by individuals without recourse to clinical measures, e.g. by heart rate responses or the sensation of breathlessness following a standardised exercise test. Raising wider awareness of the utility of such measures, for example in children and young people, may be very important in promoting cardiovascular health in the population (see below).

The aspects of the life course, in terms of detrimental or beneficial factors affecting cardiovascular resilience, are to a large extent common across functional domains. Thus smoking and obesity are risk factors for lung and cardiovascular disease, for some cancers and neurocognitive decline, and healthy diet and physical activity promote resilience and sustained function across all domains. For this reason, the application of easily quantifiable measures of function for one domain can give valuable prognostic insights into others. A good example is grip strength, for which the level predicts death from myocardial infarction, stroke, cancer, and respiratory conditions as well as falls and fractures (33).

Importance of early development

The life course perspective on CVD makes it clear that the earlier interventions to promote cardiovascular resilience are instituted, the better. This is not a new perception. The epidemiological observations of Forsdahl, Higgins et al, Wadsworth et al, Gennser et al, and, most well-known, of Barker and his group have demonstrated repeatedly that markers of adversity in early life such as birthweight, are strongly associated with greater risk of cardio metabolic disease many years later (34-39). What perhaps has been less well appreciated is that these data do not suggest that pathological changes occur *in utero* or in early childhood and are then amplified over later life. Rather, the data reveal that the developmental effects are graded across the entire normal range of, for example, birthweight for a population and are associated with the degree of risk later. This is unsurprising when we recall that CVD is so common in the population: it does not seem likely that the majority of individuals experiencing CVD had aspects of their development which were pathological as this would indicate more of a teratological effect. The developmental effects is now viewed as part of the normal responses to the early environment made by the embryo, fetus and infant, with pathophysiological effects occurring only at the extremes of an environmental challenge, such as maternal disease or placental dysfunction (40). This thinking is supported by a plethora of animal investigations, using a range of small and large species and a variety of developmental environmental challenges including over- and undernutrition, hypoxia, steroid or endocrine disruptor exposure and stress. These have all shown how development affects later cardiovascular function as well as that of all organ systems studied (41- 44).

The combination of epidemiological, animal and clinical studies led to the establishment of a new interdisciplinary field of science known as the developmental origins of health and disease (DOHaD). The field was further strengthened by involvement of developmental biologists (see for example 45) and evolutionary biologists (46). The former have made it clear that the effects of the developmental environment on later CVD risk can start even in the early embryonic phase (47-49). The latter have linked DOHaD processes to the early environmental and so called parental effects which have been well established in a range of phyla to play an adaptive role (50): this means that using developmental plasticity to alter phenotypic attributes to suit an environment may confer benefit in terms of survival to reproduce (i.e. Darwinian fitness). Such developmental plasticity is a source of naturally occurring variations in phenotypes in many species. As cardiovascular function is a major aspect of survival attributes, developmental effects on cardiovascular phenotype makes sense, at least teleologically.

An aspect of developmental plasticity which has evolved as a result of this adaptive advantage is that it permits phenotypes to develop to be fittest in the environment to which they are exposed, sometimes through their parents, during development. This was termed a “predictive adaptive response” (51) after the late Patrick Bateson’s concept of “forecasting”. The prediction is accurate, and therefore beneficial, if the critical aspects of the post-developmental environment, such as nutritional quality and abundance, match those of the developmental environment when the phenotype was established. If the later environment does not match that predicted, the individual is less well adapted and at greater risk, e.g. of CVD. Such mismatch can occur for a variety of reasons (52). One occurs if individuals are faced with an environment which poses significant health challenges to which they have not evolved to respond. There are many examples of the health effects from mismatch to such evolutionary novelty in our world today including motorised transport, fast food, digital technology etc., all of which have been associated with the increased CVD risk in contemporary societies. It is noted below that such evolutionary mismatch can also occur during the developmental phase of life itself.

A second cause of mismatch occurs when the environmental signals, on which developmentally plastic changes in phenotype are based, do not represent the current environment accurately, so that the mature organism is likely to be exposed to very different environmental challenges. The commonest cause of such mismatch is maternal disease such as hypertension, pre-eclampsia or diabetes (53), or an unbalanced maternal diet lacking key micro or macro nutrients in sufficient quantity for healthy development of the offspring. Hypertension or pre-eclampsia can be associated with placental dysfunction, which may be part of the causal link. Another example is low maternal vitamin D status which affects fetal bone development and markers of CVD risk in offspring (54,55) and which is very common in many urban environments in northern latitudes or cultures where women cover their bodies extensively when in public.

Perhaps the most prevalent, and on a global scale the most worrying, a form of mismatch occurs when critical aspects of the environment for health change rapidly between generations. This is best exemplified by the changes in diet and physical activity levels occurring with socio-economic development, and especially with urbanisation, across the world. More than 50% of the world’s population now live in urban environments, where levels of pollution, poor access to opportunities for physical activity and unhealthy diets of highly processed foods rich in fat, sugar and salt are becoming the norm. Low income countries transitioning through economic progress, as a result of several factors including reduction in the levels of communicable diseases, are particularly at risk of such mismatch. For example, the transition from under nutrition to over nutrition, with accompanying overweight and obesity, has led to a double burden of disease: the combination, malnutrition, now affects in some form 1 in 3 people globally (56). This problem is highlighted in SDG2 but addressing this challenge will be fundamental to attaining all the SDGs (57).

Mechanisms of inheritance of CVD risk

There are multiple levels at which the inheritance of CVD risk can occur. Broadly speaking, they divide into mechanisms which operate at the social or biological levels, although this distinction is somewhat artificial as so much of human biology is inextricably linked with our social structure, a fundamental aspect of our evolution (58).

CVD and other NCDs “run in families” and it is widely recognised that social inequalities affect this risk, with socio-economic status and educational attainment as important indicators (59). They are however some of the most intractable drivers of risk to change. This is partly for the reasons mentioned in the Introduction of lack of clarity on what individuals and families can do to reduce risk relatively simply, and also sometimes the lack of political will to address seemingly large and long-term problems. Whilst the evidence on the health implications of reduction in CVD risk factors is strong, policy making is a multifaceted process which must take account of the needs of a range of stakeholders. A primary consideration will be financial, and whilst the longer-term health costs of CVD and other NCDs to the State and individuals are well known, the cost of interventions versus the financial penalties of inaction are not. Policies aimed at longer term goals are always harder to prioritise, especially in areas such as cardiovascular health where there is not great pressure from the electorate to act. The focus on shorter-term goals in relation to transmission of risk across generations is important (see discussion on interventions below).

For the ‘biological’ mechanisms of inheritance of CVD risk, the most well-known are fixed genetic factors. There are several well established fixed genetic variants which are strongly associated with CVD and with pre-disposing risk factors such obesity (60,61). They may be single nucleoside polymorphisms (SNPs), multiple repeats or deletions. However, whilst inheritance of such genetic variants is highly correlated with CVD in individuals, at the population level either singly or in combination they account for only a very small fraction of risk. Thus the inherited risk of CVD attributable to such genetic variants at the population level is small even if there are strong correlations between phenotype and risk between individuals. This distinction is not widely appreciated and had been fuelled by the popularisation of a deterministic, gene-centric strand of research (e.g. 62) from studies of mono- versus dizygotic twins or adopted children. An additional, serious problem with such an approach is that it assumes that fixed genetic variation is the only important mechanism of transmission of phenotype, such as risk of CVD, from parents to children aside from shared environment. This ignores the role of parental influences on early development, especially *in utero* and in infancy, affecting offspring’s phenotype via the mechanisms of developmental plasticity: this is the field of DOHaD (63). The inclusion of more and more genetic variants with small effect sizes, derived from the study of ever larger numbers of individuals as whole genome sequencing becomes cheaper, will not address this problem. Moreover the epistatic genetic effects which can underlie such associations can make investigation of underlying pathways problematic.

The field of epigenetics has allowed many of the problems associated with studies of fixed genetic inheritance of CVD risk to be addressed, especially as epigenetics by definition focuses on the interaction between genetic and environmental factors. The most widely studied epigenetic process is DNA methylation at CpG sites, which can be distinct rather than part of clusters or CpG islands. Even the degree of methylation at single CpGs linked to mechanistically plausible genes can account for a sizeable proportion of adiposity in children (64). Other studies have shown association with CVD risk markers (65). In such studies it is important to replicate observations in other cohorts, and to show mechanistic function of an epigenetic mark in terms of gene expression. This is required because the number of possible epigenetic changes makes finding some statistically highly likely by chance alone, and the stochastic nature of epigenetic changes can mean that they may not be functionally relevant.

Epigenetic studies of tissues such as umbilical cord collected at birth have also allowed examination of the influence of factors such as maternal diet or BMI before and in pregnancy and of trajectories of adiposity in children from birth until just before puberty (66). The affect sizes from a change in DNA methylation at a single CpG are equivalent to those of a SNPs. It also becomes apparent that epigenetic changes on the offspring can be mediated even in the early embryonic period, at a time when a couple do not know that they have conceived and are influenced by aspects of paternal behaviour, mediated by epigenetic effects on the sperm (67, 68). The inheritance of cardiovascular and metabolic disease risk by epigenetic processes can be passed down to grand-offspring in both animal studies and human cohorts (see 69), but the issue is controversial (70,71).

Studies of the mechanisms of inheritance of CVD risk require clearly established stimuli or drivers of the effect on developmental plasticity in the offspring, and also clearly defined markers of outcome in the offspring – ideally markers lying on the mechanistic pathway(s). In many respects we are not yet able to meet either of these criteria fully. The role of maternal diet, usually measured in pregnancy but likely established before conception and often not much changed during pregnancy (72) is one factor. Consumption of a “prudent”, i.e. healthy, diet is clearly linked to educational attainment (73), although the particular components of the diet associated with CVD risk and epigenetic effects in the offspring are varied. An association has been shown between a low maternal carbohydrate diet in early pregnancy and methylation of one CpG in the RXRA gene at birth and child’s adiposity in six and nine year old children (64), and also between maternal BMI before and during pregnancy and adiposity longitudinally in a cohort of children from birth to eight years of age (66). Although such epigenetic marks appear to be good predictors of CVD risk, it is not known whether they are reversible post-natally as opposed to being potentially preventable prenatally. Specific components of the diet are being investigated, for example the association between oily fish intake in late pregnancy, as a source of Omega 3 PUFA, and child’s descending aortic pulse wave velocity (74).

Whilst a range of CVD risk outcomes have been measured in children, they differ in clinical relevance. Such measurements have recently been combined in the same cohort, and child’s body composition in terms both of fat and of lean mass also assessed (75). The latter measurements are important because the utility of BMI in children is limited, as both fat and lean mass contribute to it: greater fat mass may increase BMI and be associated with increased CVD risk, while greater lean mass also increases BMI but is associated with reduced CVD risk.

One of the problems in this field has been the preponderance of the use of birthweight as a marker either of prenatal nutrition and growth and/or a marker of developmental outcome. Birthweight can be a marker of these factors, but without other independent measures its utility is limited. Patterns of fetal growth are more insightful as similar birthweights can follow very different trajectories of fetal growth. Fetal growth patterns vary substantially between populations and so, although this has been discounted (76) they need to be considered in context as it is not appropriate to assume that such patterns are similar across geographical regions or ethnic groups (77,78). The significance of fetal growth patterns as a marker of development is shown by a range of studies which support the mismatch hypothesis. In a cohort from the Netherlands (79) the highest systolic and diastolic blood pressure was found in children who grew more slowly during the last trimester and faster in the six months after birth. In a study of the mismatch hypothesis in a UK cohort, those children who had grown more slowly than expected in the last part of gestation were significantly fatter than the population mean if they consumed an ‘imprudent’ diet but not if they consumed a prudent diet, as children (80). The level of adiposity in children who had grown faster than expected as late gestation fetuses independent of the quality of their childhood diet.

The mismatch hypothesis, supported by the observations above, can be viewed as only the first phase of the multigeneration transmission of CVD risks. Those individuals at greater risk as a result of mismatch between, for example, restricted fetal nutrition and abundant rich nutrition in their childhood, adolescent and early adult years, are not only more prone to develop obesity and cardiometabolic disease but to passing this risk to their children. This has been shown most convincingly for conditions such as type II diabetes or gestational diabetes mellitus, where the risk of diabetes in the offspring is substantially greater (81). The dictum “obesity begets diabesity” captures this issue, which underlines the importance of preventing the transmission of risk from one generation to subsequent generations.

Interventions to prevent inheritance of CVD risk

The discussion above about the life course trajectory of CVD risk and the transmission of this risk across generations should not be taken to imply that interventions must be long-term and cannot be considered to demonstrate short-term benefit. Quite the opposite. The research from a range of human cohorts and clinical studies emphasises that many aspects of early development which set the risk trajectory of a variety of conditions are established by the end of the first 1000 days of life, i.e. from conception until the child has reached two years of age. At the end of this period nephron and cardiomyocyte complements are complete, as is the development of elastin in many blood vessels; the trajectory of early growth and body composition influencing childhood adiposity (82); and many aspects of cognitive and emotional development (83). Hence there are a range of measurable, quantifiable childhood outcomes which could be used to assess the efficacy of potential interventions. There are in addition some low cost, easily applied, clinical tests which could help identify at risk pregnancies and thus offspring likely to be born with a higher CVD risk. A good example is the measurement of blood glucose, which has been recommended to be conducted universally in early pregnancy (84). Ideally this would be a fasting blood glucose and a glucose tolerance test, but a simpler test would be highly effective as a first-line screening tool. In time it is likely that early pregnancy tests for pre-eclampsia will be devised as well (85).

The next question which arises concerns the nature of the interventions needed. Once again this is relatively straight forward, as the aspects of parental behaviours which affect development over the first 1000 days of life of the child are well-established (86). There may be some specific nutritional components, which can have a substantial and immediate effect, especially folic acid, iron and vitamin D supplementation in women who are deficient. However these are special cases of the general principle that women of reproductive age, and their partners, should consume a balanced diet, as per widely recognised recommendations (87,88).

Despite new discoveries of the mechanisms underlying the conditioning of risk of CVD in the offspring, especially epigenetic processes, it seems unlikely that this will lead to a new phase of drug discovery for the pharmaceutical prevention of risk. Epigenetic changes are so widespread across the genome that at present it does not seem feasible to target a drug to a specific region of interest, even though there are several such regions now known. There are very few drugs licensed for use in pregnancy and childhood, for very good reason: the disaster of thalidomide still casts a very long shadow. Likewise, there are concerns about the use of new gene therapy approaches such as CRISPR to the early embryo in order to correct genetic defects (89). The absence of monogenetic causes of CVD limits the argument for such an approach in any case.

The discussion above concerns interventions made during the period of development of the offspring over the first 1000 days. It has to be said however that, with some exceptions (e.g. folic acid supplementation, smoking cessation), the trials to date aimed at modifying risk factors such as maternal BMI in pregnancy, fetal growth or infant adiposity birthweight have met with only limited success (e.g. 90-92). It is therefore important to look again at the life course trajectory of CVD risk and ask whether there is a phase during which interventions may be particularly valuable or efficacious. The answer, by all accounts, is the preconception period, which coincides with adolescence or young adulthood. The argument is that intervening at this time can confer a triple benefit in health and economic terms: it should make adolescents healthier now; it could promote their health later as adults because many lifelong health behaviour habits are established at this time; and it could promote the health of any future children which they may have (93). There are over 1.2 billion adolescents in the world today, and from a demographic point of view they will form a greater percentage of the population in the near future in LMICs in sub-Saharan Africa, even if the health concerns of many high income countries are focussed on the diseases associated with ageing. From the discussion above, it is clear that the two agendas are linked. However, adolescents as a population group receive less support for health in recent decades than other sections of the population globally. Mortality from CVD in middle age is graded across the entire population with respect to BMI in adolescence after allowing for other adult confounding factors (Israel 94). BMI in adolescence is the result of the trajectory established at the age 2 years, whether the data is viewed prospectively or retrospectively (82), supporting the 1000 days agenda discussed above.

Adolescents are the parents of tomorrow. The preconception period has been identified as the critical phase in maternal and child health (95) and is now increasingly recognised as a time when significant interventions can be made (96). This period is highlighted in SDG 3.4, and underpins many other SDG targets. Maternal health before conception can reduce the risk of childhood obesity (97). It is of concern that this period of the life course was not specifically emphasised in the United Nations Third Political Declaration on NCDs arising from the High Level Meeting in 2018.

The inheritance of CVD risk by future generations is unlikely to be minimised without a holistic strategy which engages multiple stakeholders, from policy makers, through health care providers and other professional groups, the private sector, local government and young people themselves. The last group have been particularly ignored, yet the co-creation with them of a ‘bottom up’ initiative to complement the ‘top down’ strategies of government (98) is increasingly seen as important. Adoption of healthier behaviours requires not only capability and opportunity but also motivation to do so (99). It is not appropriate to burden formal educational systems with generating this motivation. However, links between schools, hospitals and University research groups hold promise as a new opportunity (100). Such collaborations can build on enquiry skills of adolescents or younger children to engage them in greater health literacy through science literacy.

Conclusion

CVD is a very significant problem globally. Once thought to be largely due to a combination of genetic predisposition and unhealthy adult lifestyle associated with affluence, it is now recognised to have a powerful developmental component whereby susceptibility is established in early life. The underlying processes operate to a greater or lesser degree across the entire population, even in pregnancies and infancies which appear otherwise to be normal. The inheritance of CVD risk operates in all populations, including in low income countries, and will become apparent as a health, economic and humanitarian burden as other causes of mortality and morbidity such as infectious diseases are reduced.

Despite usually being classified as “non-communicable” diseases, new insights into the inheritance of CVD risk make it clear that these diseases are communicable. Labelling them as conditions which they are not may undermine the urgent priority which needs to be given to preventing such transmission. This is not only a practical, but is an ethical, concern if we are to give young people and their as yet unborn children the healthy future which they have a right to expect.

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