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Evidence
Brief

BEYOND GENES:
HOW FATHERS PLAY A BIOLOGICAL ROLE IN THE HEALTH OF FUTURE GENERATIONS

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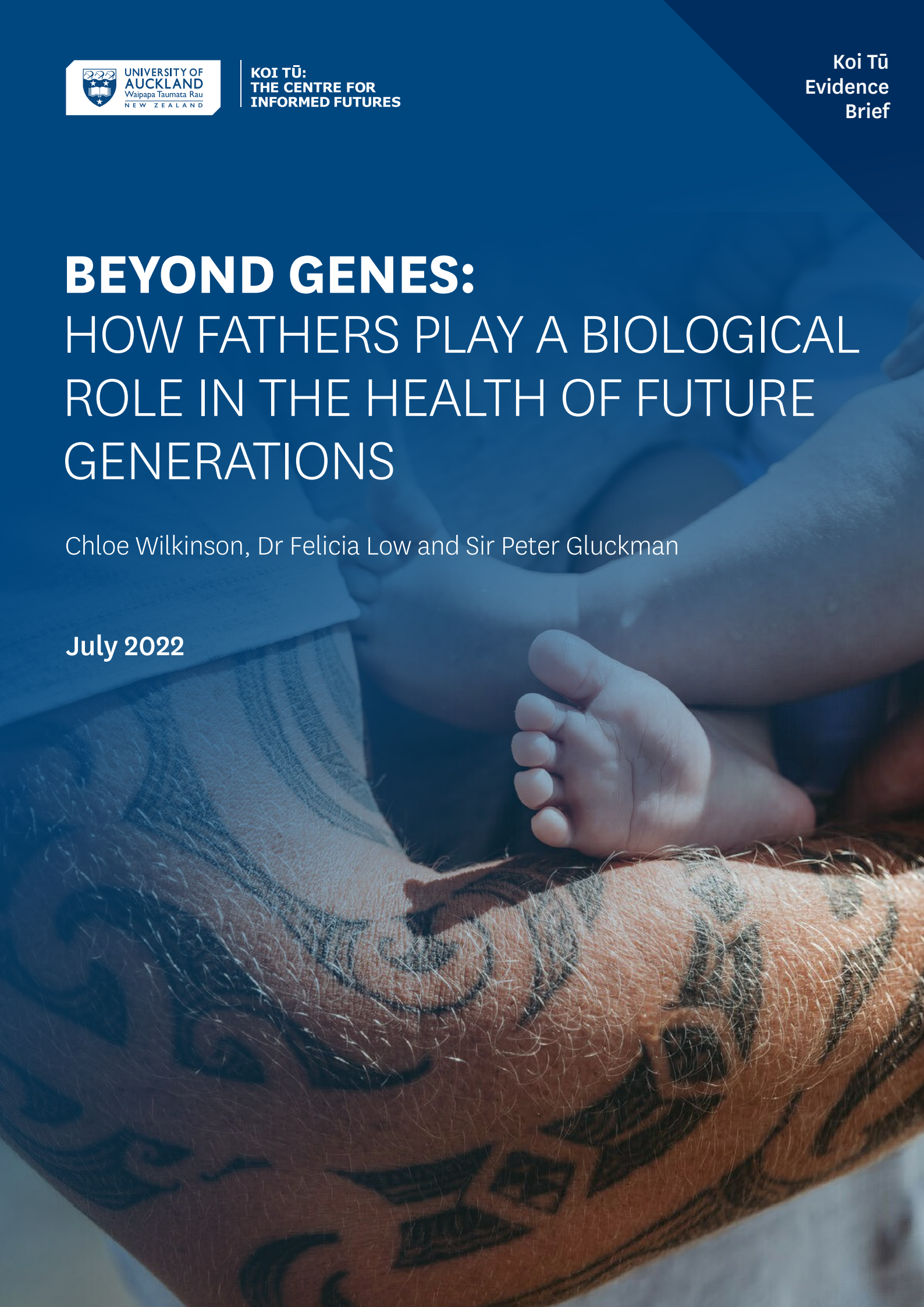

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BEYOND GENES: HOW FATHERS PLAY A BIOLOGICAL ROLE IN THE HEALTH OF FUTURE GENERATIONS

Key points

- It is well established that the environmental conditions a person is exposed to before and in the first few years after birth shape their future wellbeing, but most research and public health advice focuses on the health and lifestyle choices of women rather than considering both biological parents.
- There is growing evidence that men's health around the time they father a child exerts a biological influence on their child's health. This influence may persist across multiple generations.
- Health and wellbeing advice for men preparing to conceive should be normalised, and information about the father's role in their children's health should be conveyed to the general public and integrated into school learning programmes.
- Since the effectiveness of individual education around responsibility for one's own health is constrained by wider socioeconomic and systemic forces, population-wide approaches aimed at addressing the broader social determinants of health should be bolstered in the interests of all of society.
- Society should refocus towards promoting a shared biological and social parental responsibility for the health of future generations.

The developmental origins of health and disease

The concept of the *developmental origins of health and disease (DOHaD)* is based on observations that the environmental conditions a person is exposed to before and in the first few years after birth affect health after birth and later in life. A large body of research has unearthed connections between exposure to a range of influences such as stress and poor nutrition *in utero* and in early childhood with a host of chronic diseases in adulthood including psychiatric disorders, obesity, heart disease and type 2 diabetes.

Most DOHaD research has focused on women rather than men. This reflects a widely-held assumption that the environment a mother creates for her baby during pregnancy – through behaviours such as smoking and pre-existing factors like obesity or being of older age – strongly influences her baby's health.[1] This assumption means women bear the brunt of social disapproval if they are perceived to make choices that will harm future generations. Furthermore, the sex imbalance in the available research means that potential opportunities to improve population health by targeting information towards men may be missed.[1]

Advances in the science of epigenetics over the last two decades have changed the way inheritance is understood, and revealed that children inherit more than just DNA from their parents. It is now clear that genes in the DNA sequence have epigenetic markers that switch those genes on or off, without affecting the underlying DNA sequence.[2] The ways in which genes are turned on or off or expressed within a cell affect its function and those of other cells. Environmental factors such as stress, diet, or chemical exposure have been shown to affect sperm epigenetic markers and have effects after fertilisation thus leading to alterations in offspring gene expression (Figure 1).[3] This information has opened the door for investigations into the biological ways men might contribute to their children's health.

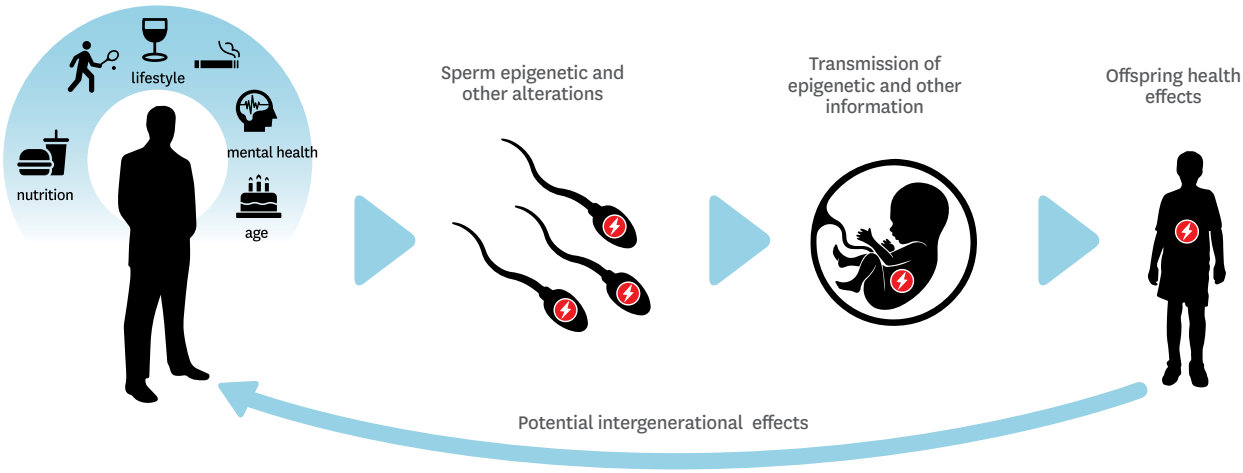

Figure 1. Potential mechanism by which paternal environmental exposures affect disease risk in children, with possible intergenerational consequences.

Understanding these potential new forms of inheritance of disease risk is important because, just as epigenetic markers are changed by environmental factors such as poor diet or stress, they can also respond positively to health and lifestyle changes such as improved diet or mental health support. Those positive changes could potentially interrupt multigenerational cycles of ill health, because animal studies have shown that epigenetic changes can persist across multiple generations, with changes in sperm and corresponding effects on offspring health observed after paternal and *grand*-paternal exposure to various environmental influences.[3-5]

Much of the existing knowledge in this field comes from animal studies, where controlled breeding in experimental environments and rapid turnaround of generations allow robust conclusions to be drawn. Evidence for epigenetic inheritance in humans is still emerging; human studies tend to be observational due to ethical and practical barriers to conducting intervention studies. Nevertheless, the combined evidence from animal and human studies points to a range of men's nutritional, health and lifestyle factors as potentially important contributors to the paternal origins of health and disease.

This evidence brief focuses on the biological aspects of the father's role in contributing to his children's health. However, this should be considered in concert with social aspects of parenting and whānau relationships; for example, the supporting partner's behaviour from before conception and into his or her child's life, including emotional support offered to the mother and the strength of their bond with the child.[6] Children are increasingly being born and raised in a diverse range of family structures, and non-biological parents or caregivers of all genders have a vital role to play in children's health and wellbeing.

Physical health and nutrition

The leading paternal physical health and lifestyle factors thought to affect children's health include bodyweight and other aspects of nutrition. High paternal weight around the time of conception correlates with clinical predictors of obesity, heart disease and diabetes in children.[7, 8] It is not clear whether these effects are due to epigenetic inheritance, genetic effects or fathers' influence on their families' diets. Paternal type 2 diabetes and poor nutrition have also been linked with negative effects on children's birth weight, risk of diabetes and other signs of metabolic health such as cholesterol levels.[7, 8] Studies of historic events have shown these effects can reach across multiple generations; for example, in a Swedish community that experienced periods of food shortage and abundance between

the late 1800s and early 1900s, boys who had an abundance of food before puberty had sons who were more prone to diabetes and grandsons with a higher risk of dying from cancer, whereas those who had limited food had grandsons who lived longer.[9-11]

Fathers may influence their children's weight in multiple ways, including shared diet and physical activity habits. However, shared habits do not fully explain observed links between paternal weight and children's birth weight, and there is growing evidence for direct (i.e., via sperm) transmission of health risk from father to child.

There are multiple examples from animal studies where offspring of fathers fed high-fat diets show signs of obesity, heart disease and type 2 diabetes that can be traced back to epigenetic changes in the fathers' sperm.[7, 12, 13] If the unhealthy diet is continued over multiple generations, excess weight and related sperm epigenetic changes accumulate.[14] Diet, weight and physical activity patterns are typically interlinked, and so too are the effects on sperm epigenetics and on offspring health outcomes. For instance, paternal exercise induces positive epigenetic changes in mouse offspring which alleviate the negative effects of poor diet and obesity. These positive changes in the offspring include enhanced brain function, lower risk of the equivalent of diabetes, better cardiovascular health and reduced body fat.[15] Animal studies have shown that even the fluid portion of semen can affect early embryo development depending on paternal diet. In mice, this fluid from males fed low-protein diets has been associated with higher body weight, glucose intolerance and gene expression patterns characteristic of liver disease in offspring.[16]

In humans, a modest body of research has reported influences of a man's weight and diet on sperm epigenetic regulators of genes implicated in weight and metabolic health. These include differences in overweight versus normal weight men,[17] relationships between paternal obesity and epigenetic markers found in babies and young children,[18, 19] and correlations between frequent consumption of fatty foods such as pizza and fries and increased likelihood of sperm epigenetic changes.[12] Importantly, differences have been found in epigenetic profiles of sperm taken from men before and after surgery for weight loss,[20] and before and after a six-week diet enrichment with a supplement high in vitamin D and healthy fatty acids.[21] These studies provide evidence that epigenetic modifications respond to improvements in nutrition, which suggests that improving a man's diet and lifestyle may prevent or reduce transmission of health risk to his children.

Mental health

It has long been thought that parents with mental health disorders can pass a tendency of poor mental health to their children. While many studies focus on maternal mental health, those looking at fathers report effects that are independent of the mother's mental state. Aspects of paternal mental health that have been examined include depression, anxiety, bipolar disorder and post-traumatic stress disorder. They appear to have effects on children ranging from an increase in very young children's negative behaviours and emotions to symptoms of psychiatric disorders in adults.[22] For example, in a follow-up of almost 60,000 Finnish children born in 1987, those whose fathers had previously been hospitalised for a psychiatric illness were twice as likely to be diagnosed with a mental disorder by age 21 (Figure 2).[23] Studies of war and genocide have also identified effects of paternal trauma on their offspring; for instance, adult children of men who served in the Vietnam war are more likely to experience anxiety, depression, self-harm and suicidal thoughts compared with children whose fathers were in the army but were not deployed to war.[24, 25]

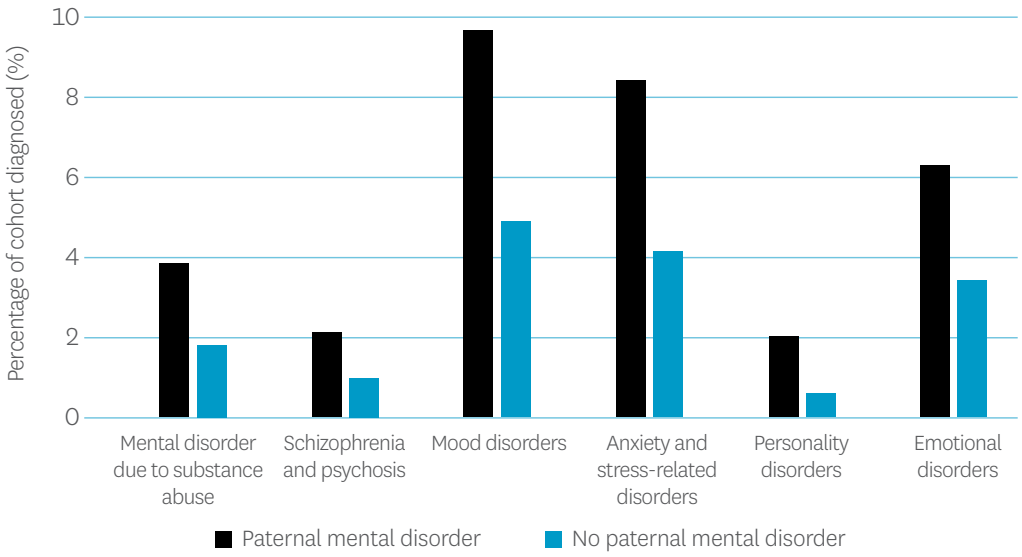

Figure 2: Comparison of the percentage of a Finnish birth cohort diagnosed with a mental disorder whose fathers also had a mental disorder, compared with those whose fathers had no mental disorder. Adapted from Paananen et al.[23]

The mechanisms behind the transmission of mental health risk likely involve a combination of genetic inheritance, epigenetics and behavioural factors related to how the father interacts with his family.[22, 25] Animal studies have shown that offspring of fathers subjected to stress or trauma are more susceptible to symptoms of depression and anxiety, and that this susceptibility is transmitted through sperm.[26-29] Such signs of depression and related behaviours in offspring can persist across at least four generations.[30] The timing and type of exposure may be relevant, with some studies suggesting that stress has more impact on offspring if it is chronic rather than acute or experienced early in the father's life.[29] Importantly, it has also been demonstrated that epigenetic dysregulation in mouse sperm occurring as a result of early-life stress can be reversed through positive changes to the mouse's later physical and social environment, thereby interrupting the transfer of stress signals to the next generation.[31]

A small number of human studies have also demonstrated epigenetic changes as a result of stress or trauma. Men who experienced adverse childhood experiences have been found to have altered sperm epigenetic markers.[32] In a recent study, associations were found between men's histories of early life trauma and the pattern of epigenetic markers in their children's blood.[33]

Age

Advanced paternal age at conception (defined as anywhere between 35 to 45, depending on the study) has been associated with a range of effects on children's health including an increased chance of premature birth, low birth weight, chromosomal disorders and psychiatric/mental disorders. There is also some evidence pointing to a higher frequency of birth defects such as cleft palate and more complicated pregnancies and childbirths.[34, 35] These associations are independent of the mother's age, suggesting they are mediated by sperm.

An increased likelihood of psychiatric disorders, mainly autism spectrum disorder and schizophrenia, is well documented in children of older fathers. A synthesis of multiple studies found that a 10-year increase in paternal age was associated with a 21% higher chance of autism in children.[36] Regarding schizophrenia, a 2021 review reported that an increased risk starts to become significant for children born when their fathers were in their mid-to-late 30s and becomes stronger with increasing age, with up to a fivefold increase in risk when fathers were aged 50 or above.[37] There is also some evidence of

persistence across generations, with a grandfather's age linked to both autism and schizophrenia in his grandchildren.[38, 39]

The risks observed with higher paternal age are thought to result from biological processes associated with aging. These include reduced sperm quality and epigenetic changes in sperm.[34, 35] Another important contributor appears to be the large number of *de novo* (newly arising) mutations occurring in older men. *De novo* mutations happen as sperm or egg cells are formed and lead to genetic changes in children that are not present in the parent. While the number of de novo mutations found in egg cells increases only slowly over a woman's reproductive lifetime, sperm cells have been found to contain many more mutations than egg cells and, crucially, the number of mutations increases progressively as men age (Figure 3).[40, 41]

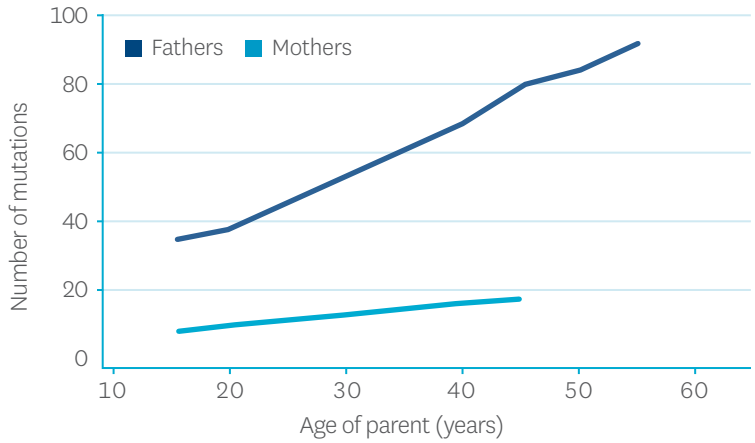

Figure 3: The relationship between the age of mothers and fathers at the time of their child's conception and number of *de novo* mutations identified from either parent. Adapted from Jónsson et al.[40]

De novo mutations have long been known to cause various diseases and genetic disorders. A group of developmental disorders caused by *de novo* mutations, such as achondroplasia, Noonan syndrome and Costello syndrome, have been shown to be so closely linked to increased paternal age that they are known as paternal age effect disorders.[42] Research indicates that both *de novo* mutations and altered paternal sperm epigenetics may be responsible for some occurrences of psychiatric disorders including autism spectrum disorder and schizophrenia in offspring.[41-45]

Alcohol, tobacco and illicit drug use

The effects on children's health of paternal alcohol exposure prior to conception have been studied for over 100 years, and a range of negative outcomes in humans and other animals have been reported.[46, 47] In humans, it confers a moderately higher chance of congenital heart defects, with a systematic review calculating that children whose fathers had a history of alcohol exposure in the three months prior to conception were 1.44 times more likely to be born with a heart defect.[48] There is also evidence pointing to an increased chance of birth defects including cleft lip or palate, miscarriage and low birth weight.[47, 49-51] In animal studies, paternal alcohol exposure produces symptoms in offspring that are also seen in attention-deficit hyperactivity disorder (ADHD) and fetal alcohol spectrum disorder. These include impaired learning, increased anxiety and impulsiveness, and low birth weight.[47, 52, 53]

Evidence from both human and animal studies suggests that paternal alcohol exposure prior to conception can adversely affect offspring's attitudes and sensitivity towards alcohol, and produce behaviours in offspring that are commonly seen in animals under chronic stress.[47, 54] Reduced sensitivity

to alcohol is a risk factor for developing alcohol-use disorder and has been identified in children of alcoholic fathers.[55] These children, particularly sons, have a higher likelihood of developing alcohol-use disorder themselves, as well as a range of other brain and behavioural problems.[55]

A range of potential alcohol-related effects on sperm epigenetics have been identified.[47, 52] In one mouse study, ongoing alcohol exposure changed several sperm epigenetic patterns, including in regions of the genome thought to play a role in father-child epigenetic transmission.[56] Other studies have identified differences in sperm epigenetic markers potentially relating to stress and ADHD.[46, 53]

Paternal recreational drug use around the time of conception is under-researched but is also implicated in offspring health and developmental outcomes. A review identified a small collection of research, mostly focused on cocaine or cannabis.[57] Paternal cocaine exposure had mixed effects on birth weight in animal studies, but doubled the risk of offspring heart defects in human studies. Paternal cannabis exposure has been linked with various congenital abnormalities and mild cognitive impairment in animal offspring, and with increased risks of heart defects, a specific form of sarcoma, and sudden infant death in humans.[57] A small number of animal studies are available and suggest potential for intergenerational effects of paternal cannabis exposure on offspring growth and ability to pay attention.[58, 59] Two human studies identified sperm epigenetic patterns in male cannabis users that were similar to those seen in cannabis-exposed rodents and involved genetic pathways relating to early life development and autism spectrum disorder.[58, 60]

Cigarette smoking by fathers before conception and during pregnancy has been linked with moderately increased risks of congenital heart disease, limb and digestive tract abnormalities, cancer, asthma and neural tube defects in their children.[61-65] For example, a systematic review concluded that children whose fathers smoked were 1.68 times more likely to have a neural tube defect and that the risk increased in line with the number of cigarettes smoked per day.[61] A long-running British longitudinal study recently reported that boys whose fathers started smoking before puberty, and girls whose grandfathers or great-grandfathers smoked before puberty, had increased body fat during childhood and into early adulthood.[66] Tobacco smoke damages the DNA of developing sperm cells, causing chromosomal abnormalities and *de novo* mutations which may be passed to children.[65] Exposure to cigarette smoke has been found to affect animal sperm epigenetic regulation.[67-69] There is also growing evidence of sperm epigenetic changes in men who smoke, and isolated examples of measurable epigenetic changes in blood samples from young and adult children of male smokers.[64, 70-73]

Why this matters in New Zealand

Like most high-income countries, New Zealand has concerning rates of obesity and non-communicable disease. According to the 2020/2021 New Zealand health survey, three-quarters of men aged 15 and over have diets lacking in fruit and vegetables, and seven out of ten are overweight or obese. Fifteen percent have been diagnosed with a mood and/or anxiety disorder. Over 80% drink alcohol and 27% meet the New Zealand health survey definition of hazardous drinkers. Eighteen percent of men report using cannabis in the prior 12 months. A large amount of public policy work has been done to reduce tobacco use; however, 11% of men currently smoke.[74] Around 10% of men, and almost one quarter of those aged 18–24, use electronic cigarettes (vapes) at least once a month,[74] and the potential impacts of this on child health are not yet known. Furthermore, the average age of New Zealand fathers has risen since records began in 1980 (Figure 4).

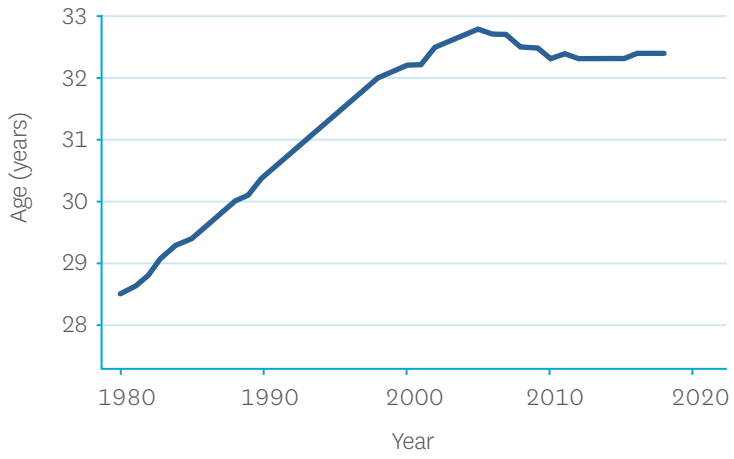

Figure 4: Median age of New Zealand fathers at the time of the birth of their child, from 1980 to 2018. Adapted from Statistics New Zealand.[75]

A significant proportion of New Zealand biological fathers thus have factors putting them at risk of adversely affecting the health status of their children, and ingrained assumptions around women as the sole contributing parent to a child's early growth and development are no longer valid. Additionally, Māori and Pacific men tend to be overrepresented in statistics relating to obesity, psychological distress, smoking and hazardous alcohol use. The accumulating evidence for paternal effects and the impact on intergenerational health therefore offer a compelling basis for policymakers, and indeed the medical profession and general public, to act on this information.

Implications for society, the health system and the education system

The available evidence suggests an important paternal biological influence on children's health. The public health implications therefore warrant consideration of three recommendations:

1. Public health educational campaigns

Policymakers should consider health educational campaigns to share information about the role fathers play in the health of their children even before conception. While men are capable of fathering children at a wide range of ages, they may not routinely access primary health care, and in New Zealand about 50% of pregnancies are unplanned.[76] Men are currently missing out on information about potential intergenerational ramifications of their health status and lifestyle behaviours. In addition, much of the current information about the preconception period available on websites that men might access, such as the Ministry of Health's 'Advice for dads' page or Health Navigator's 'Planning for pregnancy' page, contains either brief advice about "remaining well for your baby" or focuses on factors affecting fertility.[77, 78] This can lead men to unwittingly believe that their health and lifestyle exposures have no longer-term impact beyond the ability to achieve conception.

2. Routine advice for intending fathers

Primary health providers should implement routine advice for men about preparing to conceive a child that goes beyond guidance for improving fertility. Many of the recommendations that might form part of this counselling, for example to maintain a healthy weight or abstain from smoking, are already included in general population health advice. However, reframing these recommendations will have specific impact and will ensure men are fully informed, as is their right as consumers of a healthcare service. This will provide an opportunity for men to proactively plan for health and lifestyle improvements in advance of starting a family. Such improvements are likely to be effective even over a period of months prior to conception, so intending fathers should be reassured that if

maintaining such behaviours over a sustained period feels unachievable, short-term changes are still beneficial.

3. School learning programmes

The concept of paternal origins of health and disease should be integrated into school learning programmes, especially as habits and behaviours developed during the adolescent years track through to adulthood and influence periconceptional health and environmental exposures.[79] The Liggins Institute at the University of Auckland has partnered with schools to implement the Healthy Start to Life Education for Adolescents Project, a learning programme designed to facilitate the development of scientific and health literacy.[80, 81] This programme introduces students to simple DOHaD concepts, but there remains scope for a greater focus on boys, men and their role in future generations' health.

These recommendations need to be considered within the wider context of two further points. Firstly, much of public health policy tends to be based on individuals taking responsibility for their own health behaviours. However, a person's ability to make healthy choices depends not only on their level of knowledge, but also their capability and opportunity.[82] If money, time or other resources are scarce, a person's choices can be effectively made for them by the greater availability and affordability of less healthy options. This is particularly relevant for members of our most deprived communities, who are typically more likely to have one or more of the health and lifestyle factors that place their children at greater health risk. To achieve transformative change, population-wide approaches aimed at addressing the broader social determinants of health are needed to complement individual-level interventions. This will benefit the health of whole of society – men, women and children.

Secondly, the prevailing social discourse reflected in news articles, opinion pieces and public health advice has tended to focus on women and their childbearing behaviours. This could be seen to place the burden of responsibility for future generations disproportionately onto one sex, and pregnant women are subjected to a level of public scrutiny which has real consequences in terms of limiting their autonomy, such as their choice of food or drink.[83] Women tend to experience social disapproval regarding having babies later in life, and in some companies are being offered egg freezing as a work perk instead of more parent-friendly workplace policies.[84, 85] Meanwhile, the average age of New Zealand fathers has also increased without the same level of public pressure around the male biological clock, and men tend not to receive public judgement about the effect their choices may have on their future children. At a societal level, wider awareness of the concept of the developmental origins of health and disease, and the role both men and women play in their children's health, is needed to help normalise shared responsibility for offspring health. Better integration of these concepts into practice within our medical, education and policy communities will advance public health.

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