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Review

Determinants of male health: the interaction of biological and social factors

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Abstract

This review discusses the social and biological factors that may influence male development from conception to adulthood and also underlie the development of health disorders. It will provide assistance to those who may be considering the formulation of a male health policy. It aims to emphasize that social determinants function on a biological background that is profoundly influenced by a male's genome, inherited from his parents. The importance of the male-specific reproductive disorders is emphasized, but these also affect somatic structures through the secretion of androgens secreted from the testes. In turn, the function of the cardiovascular and nervous systems can significantly influence reproductive processes such as erectile dysfunction.

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1 Introduction

There is increasing discussion and interest about Men's Health and governments have or are developing policies related to the promotion of better health for men. These approaches are stimulated by the fact that despite increasing longevity for both men and women, men still have a shorter lifespan. For instance, in Australia, during the period 2005–2007, male life expectancy was 79 years compared with 83.7 years in females [1]. Premature death is also more common in men, with 22% of male deaths occurring in the 25–64-year-old group compared with 14% in females of comparable ages [1]. Further, there are clear differences in the causes of mortality between men and women at different ages.

The increasing financial burden of health care is also stimulating interest in approaches that can prevent disease by a variety of measures. Any attempt at prevention must be based on an understanding of the causes of ill health in the male population, without which an evidence-based approach is not feasible. This paper undertakes a review of the factors that affect optimal male health and the development of disorders that affect morbidity and mortality.

It is appropriate to consider the issue of terminology briefly. The term 'Men's Health' carries with it an implication that the topic deals with the health of adult males and is not inclusive of the fetal, childhood and pubertal health of males. For this reason, and from the very strong evidence that fetal, childhood and adolescent issues can significantly influence the health of the adult and aging males, the preferred term is 'male health'.

There is strong evidence that socio-economic factors have an impact on the health of both males and females and must be taken into consideration in any analysis of policies that impact on male health [2]. Before considering how the biological and social determinants interact to determine male health, it is important to provide a definition of male health. The

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latter could be defined as 'The optimum state of mind and body that enables a man to engage fully with his family and the society in which he lives for at least the average life expectancy of the male population'. This review will consider the manner in which the social and biological determinants of male health interact throughout the lifetime of males [3].

2 The biological and social determinants of male health

The drivers of health are many and varied, but some factors are fundamental and therefore require greater emphasis. Perhaps the most fundamental factor is the genetic constitution of a male; namely, that man's genome. This is critical because it establishes the genetic template that determines a person's sex and also the genetic propensity for disease, both of which can be influenced by a series of factors. It is likely that the capacity to analyze each person's genome is rapidly approaching and is likely to generate information that will further enable the understanding of how genetic variation will influence the quality of a male's health.

A number of factors may interact with a male's genome to determine his health. The expression and function of this genetic background is conditioned by prenatal factors operating during intra-uterine life, the 'conditioning' provided by his family, his education and his lifetime experiences [4–8]. For example, societal experiences can influence a male's approach to health, such as peer pressure to experiment with alcohol or drugs.

2.1 Occupational exposure

Through occupational exposures or the location of his home, a male can experience exposure to environmental factors that can influence disease processes. New evidence suggests that some of these influences can be transmitted to the next generation by causing mutations in his genome [9]. However, epigenetic changes that do not alter an individual's genetic code but may alter the relative expression of certain genes can occur and also may represent mechanisms by which environmental factors affect health.

2.2 Gender-specific and non-gender-specific diseases

There are gender-specific diseases that affect the male reproductive organs, and those that are termed non-gender specific that affect organs common to both men and women, although these disease processes can show differing frequencies and severities between the sexes.

2.3 The male genome

The fusion of genetic material derived from the sperm with genetic materials derived from the nucleus of the ovum and its mitochondria, the latter providing mitochondrial DNA since the mitochondria found in the mid-piece of the sperm do not gain entry to the ovum, together form a male's genome. Each man's genome so formed contains DNA derived from his parents that may harbour mutations or polymorphisms that can influence phenotypic outcomes.

2.4 The determination of male sex

The Y chromosome determines the development of the testis and, through the fetal secretion of the androgenic hormones testosterone and dihydrotestosterone, causes differentiation of the external genitalia to form the penis and scrotum [10].

New data indicate that the sex-determining genes on the Y chromosome are expressed in the brain before the testis is formed and therefore before testosterone is secreted by the fetal testis [11]. This neural expression of sex-determining genes early in gestation indicates that some aspects of male patterning do not require testicular testosterone production [12]. These data suggest that traits or behaviour may be influenced without the action of testosterone. However, this conclusion may need to be re-examined since recent data have indicated that mouse embryonic stem cells expressed the enzymes involved in testosterone synthesis and also produced measurable levels of testosterone [13]. That study provided data to indicate that testosterone could also influence the capacity of mouse embryonic stem cells to form cardio-myocytes.

The X chromosome of a male is derived from his mother, labelled Xm to designate its origin. Data regarding the inheritance of the X chromosome have provided support for possible epigenetic mechanisms that may operate via the inheritance of the X chromosome [14, 15]. Of the two female X chromosomes, one is maternally derived and is designated as Xm, and the other paternally derived, designated as Xp. Both the Xm and the Xp chromosomes contain the same genes, some of which influence social cognition such as verbal skills, higher-order executive function and skills mediating social interactions. However, the copies of these genes on the maternally derived Xm may not be expressed at the same level as those on Xp, which is paternally derived, because they are 'imprinted' [14].

This concept emerged from the study of women

with Turner's syndrome who only have one X chromosome that could have come from either the mother or the father. Women with Turner's syndrome with a paternally derived X chromosome, Xp, were better adjusted, had superior verbal skills and higher-order executive function skills that mediate social interactions than the women with Turner's syndrome who had a maternally derived X chromosome [14–16]. This phenomenon is an excellent example of 'genetic imprinting' wherein information is transferred from one generation to another without disturbing the genetic code but is transmitted by alterations in the degree of methylation of DNA and the structure of chromatin.

2.5 Sex chromosomal disorders

Sex chromosomal disorders such as Klinefelter's syndrome, wherein at least one additional X chromosome constitutes the affected male's genome (XXY), results in very small testes associated with infertility due to disrupted spermatogenesis and androgen secretion. This condition is also associated with variable learning difficulties and behavioural disturbances [17, 18]. Although a careful assessment of testicular size at the average age of conclusion of normal puberty would establish the diagnosis, about 60% of such men are never diagnosed [19].

2.6 Intra-uterine environmental exposure

There is clear evidence that the exposure of the fetus to alcohol by maternal drinking will result in the fetal alcohol syndrome [20].

What is less recognized is the influence of parental exposure to environmental toxicants and their influence on future generations, actions that are likely to be expressed through epigenetic mechanisms. For instance, in Serveso, a factory explosion exposed a significant population in central Europe to dioxin [21, 22]. For many years later, those couples closest to the explosion had a distortion of the sex ratio of children born such that the number of male children born decreased to approximately 35% compared with an almost 50/50 ratio. Another example is the subfertility in male rats born to mothers who were exposed during pregnancy to vinclodin, a fungicide used in the wine industry [23]. What was more remarkable was the fact that this effect continued for several generations after the initial exposure and it is proposed that this effect is manifested by changes in DNA methylation [24]. Further studies are required to confirm the latter results and to firmly establish the epigenetic mechanism of transmission.

2.7 The Barker hypothesis

There is increasing recognition that intra-uterine life can influence the health of children well into their adult years although the mechanisms through which these occur are, as yet, unclear. These form the basis of the Barker Hypothesis, which links undernutrition in utero, leading to low birth weight, with an increased risk of hypertension, coronary artery disease, stroke, diabetes and the metabolic syndrome in adulthood [25–27]. These may be the result of impaired nephrogenesis and a greater susceptibility to renal disease, impaired development of the endothelium and increased sensitivity to glucocorticoid hormones. Given that this *in utero* 'environmental status' affects the function many years later, there is a strong possibility that the mechanism will involve imprinting of genes [28]. Further, in addition to low birth weight, a low growth rate during the first 6 months of life can increase the risk of an atherogenic lipid profile and the development of impaired glucose tolerance later in life.

2.8 The impact of postnatal factors of male health

Postnatal development, infancy and childhood experiences are increasingly being recognized as important in the development of the brain and the behavioural patterns. Less than optimal stimulation of infants as well as parenting and access to education may affect the intellectual development and capacity of an individual to interact with society [4, 8]. Parental example can influence attitudes to the development of healthy life styles and, in turn, can result in the development of obesity and its attendant consequences, such as the development of type 2 diabetes. Although education within the school community may be able to compensate for poor parenting skills and guidance, the benefits of these two sectors functioning in concert are clearly of great value to the individual concerned.

The journey through puberty can be hazardous for many, with the challenges of peer pressure causing conflict with parental values on such issues as smoking and alcohol and the ever-present exposure to drugs of varying types. All of these external influences bear upon an individual who is experiencing the effects of his pubertal surge in testosterone production with its well-established actions on growth, muscular strength, sexual development and behaviour. The challenges of dealing with sexuality, the risk of pregnancy and the

possibility of sexually transmitted disease, as well as the increasing level of responsibility in decision making required in a variety of life events such as scholastic pathways and future careers, can all lead to significant levels of stress in individuals who do not have support systems at home and at school. All of these issues act on the genetic template and the same external influences, exerted on individuals with different genomes, can have profoundly different outcomes.

2.9 Postnatal environmental exposure

There are many examples of exposure to environmental toxicants causing disease or death. It is well known that exposure to asbestos causes the development of mesothelioma of the lungs and ultimately death. Further, the development of silicosis and pulmonary fibrosis in miners exposed to coal-mining dusts causes considerable ill health in later life, leading to chronic obstructive pulmonary disease and similarly, the smoking of tobacco results in lung cancer. All of these have led to public health initiatives that have changed the health outcomes.

There are many substances that are being recognized as causing ill health or premature death and cannot be considered in depth in this brief overview.

3 What are the issues confronting adult men that should be represented in a male health policy?

It is clear that the advances in medical care have extended the lifespan of both men and women, but in Australia, the 7-year difference in lifespan between the sexes in the 1970s has narrowed slightly to about 4 years in 2005 [1]. Setting aside the health issues related to the reproductive organs of men and women, there is a greater propensity for men to have higher rates of all forms of cardiovascular disease and many forms of cancer.

The reasons remain unclear, but clearly may be related to the male genome and to the levels of two key hormones that differentiate men from women, namely testosterone and dihydrotestosterone. The issues that remain unanswered relate to the balance, on one hand between the biological determinants of male behaviour such as their genetic status and, on the other hand, the psycho-social and environmental determinants.

In Australia, it is recognized that the issues of cardiovascular disease, including stroke and hypertension, linked to obesity and diabetes, together with cancer, are the largest causes of male mortality, representing about 66% [1]. However, the causes of mortality in men under 34 years of age include accidents, which accounted for 35.5%, and suicide, which accounted for 30.6% [1]. These differences clearly require different male health policies. The high rate of suicide brings into prominence the important issues of depression and mental illness and the need to inform policy development, which not only deals with the immediacy of those issues but also addresses the developmental and societal processes that make men more vulnerable to these risks.

3.1 Obesity

Today, the epidemic of obesity is causing great concern in many countries across the globe. In Australia, 20% of men were obese and another 44% were overweight, as found in a randomly sampled population of 6 000 men in Australia aged from 40 to over 70 years who participated in a telephone interview, and from a part of the men in the Australia Telephone Survey or MATeS study [29]. This finding is a major cause for concern because of the links between obesity and diabetes and cardiovascular disease. A 2007 report from the Office of the Chief Scientist in the UK projected that the rates of obesity in the UK by 2050 would be 60% in men, 45% in women and 30% in children, and that this would add £50 billion annually to their health budget [30].

3.2 Dementia

The other major issue that affects the ageing male and female population today is that of dementia, including Alzheimer's disease, with figures suggesting that by 85 years there is a 1 in 4 chance of developing dementia. The answers in this area are not yet available, but the continuation of mental stimulation has been proposed, but not yet proven, as a potential way of delaying the onset. Any policy developed today must ensure that these issues are addressed.

3.3 Andrological disorders

As indicated earlier, the Y chromosome establishes male sexual differentiation and the formation of the testis, epididymis and accessory sex glands, the prostate and seminal vesicles and the penis. The disorders of these organs and the variation in the levels of production of the androgens secreted by the testis define a group of disorders that form the discipline of andrology.

These disorders can impact on males at all ages of their life. In the younger population, disorders of genital differentiation, testicular cancer, male infertility and

sexually transmitted disease are major issues. During fetal life, the failure of testicular development, problems of secretion of androgens or their detection by defective androgen receptors can lead to a variety of abnormalities of the male external genitalia. In some genetic males, androgen insensitivity resulting from mutations of the androgen receptor gene can result in external genitalia that cannot be distinguished from normal females [31].

3.4 Failure of testicular descent

This disorder is common with testicular maldescent of varying degrees being present in 4%–5% of males at birth and declining to 1%–2% by 12 weeks, after which spontaneous descent is rare [32]. Higher rates of testicular cancer and male infertility are found in men with maldescent of the testes if untreated and the risk of testicular cancer persists despite successful orchidopexy [33]. Consequently, a male health policy should identify ways in which continuity of care, education of the person and his parents, and the effective transfer of information between paediatricians and general practitioners are priorities.

3.5 Sexually transmitted diseases

The occurrence of genital herpes, gonorrhoea, syphilis and HIV constitute a burden of disease that requires attention in male health policies with a very significant emphasis on prevention through adequate barrier protection by the use of condoms and effective diagnosis and prompt treatment of episodes.

3.6 Male infertility

Estimates of the frequency of male infertility are difficult to obtain as adequate sampling for prevalence studies is difficult. Data regarding Australia from the MATeS study identified that 7.8% of the men sampled were in involuntary infertile relationships, but it was not possible to determine what proportion of that infertility burden was associated with the male partner [29]. Effective management is difficult in that in approximately 40% of the men with abnormal semen analyses the cause remains unknown. Such a figure points to the need for further research as to the causative factors in the hope of developing effective modes of stimulating sperm counts and motility. A thorough assessment is required, since chromosomal defects such as Klinefelter's syndrome and Y chromosome genetic deletions are common, the latter being found in 3%–8% of men with sperm counts less than 1 million mL^{-1} [34]. Further, some men with infertility will have significant reductions of testis size and may have impaired androgen production [35].

In older men, the prevalence data indicate a significant burden of disease, particularly in older men, related to the prostate gland, erectile dysfunction and androgen deficiency.

3.7 Prostate disease

In Australia, the MATeS study identified that 38% of men have some form of prostate disease by age 70 years and the 2006 figures indicate that about 18 500 men were diagnosed as having prostate cancer [29]. These data represent a very significant burden of disease for health budgets, especially in countries with aging populations.

It is of interest that 50% of the 6 000 men in the MATeS study over 40 years had had a digital rectal examination and a prostate-specific antigen (PSA) test, this number increasing to 70% in men over 70 years. These data clearly indicate that men are willing to consider testing for prostate cancer as part of a proactive program. The treatment options arising from that testing, should prostate cancer be diagnosed, are controversial and complex, requiring careful consideration and counselling. Recent studies have provided data that are causing continued debate about the value of the PSA test due to its sensitivity but lack of specificity [36, 37]. Future research is needed to provide diagnostic tests that can identify which cancer diagnosed by PSA testing is likely to remain indolent or to become aggressive and metastasize.

3.8 Erectile dysfunction

With an extended healthy lifespan, men continue to be sexually active, with 37% of men reporting sexual activity beyond 70 years [29]. In this context, it is important to note that approximately 70% of men at that age have problems of erectile dysfunction. It is of note that despite 80% of the men sampled indicating that they would be concerned if they developed erectile dysfunction, only 30% of those with erectile dysfunction had discussed this with a doctor. This is a significant concern because of the association of erectile dysfunction with cardiovascular disease and obesity [38]. Further, a prospective study that evaluated over 9 000 men showed that when men were followed after their first episode of moderate erectile dysfunction, within 12 months 2% had a major cardiovascular event and within 5 years this figure rose to 11% [39]. They concluded that in men over 55 years, erectile dysfunction can be a predictor of cardiovascular disease and that they

have a 50% higher chance of developing cardiovascular disease. This risk appears to be even greater in younger men who have erectile dysfunction [40]. In keeping with this view, a study of indigenous Australian men identified that the rate of erectile dysfunction was 40%, about double the prevalence rate in the general Australian population, consistent with the high rates of cardiovascular and renal disease and diabetes in their communities [41]. These data indicate that inquiry about erectile dysfunction is a window into the cardiovascular system and failure to report such a symptom may miss a valuable predictor of cardiovascular disease. This reticence to discuss issues of sexuality contrasts with the acceptability of consultations and tests for prostate cancer in the Australian population.

3.9 Androgen deficiency

The rate of androgen deficiency in the entire male population is estimated to be about one in 200. However, physiological data indicate that testosterone levels peak between 25–30 years and then decline at about 1% per year [42]. The rate of decline is increased by obesity, smoking and testicular disease. The frequency of androgen deficiency in aging men has been estimated to range from 5% at 60 years [43] to higher levels in the Massachusetts Male Ageing study of 26% at 60–69 years and 31% between 70–81 years [44].

While androgen deficiency clearly affects libido, its links to non-reproductive health issues are now emerging. Diminished quality of life and poorly definable issues such as tiredness, mood swings and hot flushes may be a reflection of androgen deficiency. However, recent studies indicate that obesity increases the conversion of testosterone to estrogens by aromatase, the enzyme necessary for this conversion, which is found in adipose tissue [45]. Androgen deficiency in obese men can predict the development of insulin resistance and the likelihood of the development of type 2 diabetes. Further, in about 40% of obese type 2 diabetics, testosterone levels were low and testosterone treatment improved the sensitivity to insulin and diabetic control as reflected by lower HbA1C levels, decreased visceral fat and lowered cholesterol levels [46].

Testosterone is also critical in the development of peak bone mass, and androgen deficiency in older men is a cause of osteoporosis, resulting in fractures about 10 years later than those noted in postmenopausal women [47]. The MATeS study identified that only 1.5% of the 6 000 men over 40 years were on androgen treatment, indicating that many cases of androgen deficiency are missed, since androgen deficiency occurs in 6%–31% of men over 70 years [29, 38].

The MATeS study is a cross-sectional, self-reported health assessment of men over 40 years of age. It is critical that longitudinal studies of men, commencing at a younger age, that include clinical assessments of selected cohorts are initiated to provide data that define how identified risk factors impact on health outcomes later in life. Such a study has commenced in the European Union and the results are awaited with interest [48].

It is important to note that the issues canvassed and figures quoted in this brief review are those of a developed country. Each country will have differing profiles of male health, morbidity and mortality, which are impacted by the range of factors described earlier. Further, in developing countries, the issues of clean water, nutrition, infectious disease and malaria can profoundly alter the critical issues determining the health of males. This brief traverse across a wide range of fields that impact on male health can set the scene, but should clearly be applied within the educational and economic framework of each country.

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