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REVIEW ARTICLE

Schizophrenia Mortality: Barriers to Progress

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Abstract
Individuals with schizophrenia die, on average, 20 years before their peers, with 'natural causes' accounting for 80% of premature deaths. The aim of this narrative review is to address this phenomenon from the perspective of known factors that contribute to long life. The relevant literature from the last decade was searched in PubMed and Google Scholar databases. Four factors have been shown to be common to centarians, people who live to be a hundred: genes, life style behaviors that favor a healthy heart, social support, and a subjective purpose in life. The latter three factors are potentially modifiable but, in the context of schizophrenia, there are barriers to change, namely poverty, illness symptoms, stress, stigma, and side effects of antipsychotic medication. Barriers to change need to be addressed before substantial progress can be made in increasing the health and mortality risk of people with schizophrenia.

Keywords Schizophrenia · Mortality · Centarians · Poverty · Symptoms · Stress · Stigma · Antipsychotics

Individuals with a diagnosis of schizophrenia die, on average, 20 years before their peers and the implications behind this statistic have rightly been called a public health scandal [1]. The high mortality rate in this population has been attributed to suicide, accidental death and injury, all understandable in the context of schizophrenic illness [2]. What is less understandable is the 80% of premature schizophrenia deaths that result from 'natural' causes, mainly heart disease. There have been various speculations as to their origin. Is it because antipsychotic medications predispose to weight gain, metabolic problems and cardiovascular sequelae [3, 4]? Is it because individuals with schizophrenia engage in unhealthy lifestyles – poor diet, lack of physical activity, cigarette smoking, substance abuse, lack of self-care, non-participation in illness prevention programs such as flu shots and cancer screening [5]? Is schizophrenia a disease of accelerated aging [6]? Do genes that heighten the risk for schizophrenia commonly travel with risk genes for

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immune, metabolic and cardiovascular problems [7, 8]? Does mental health stigma interfere with access to timely and high quality health care so that normally treatable illness is left too long unchecked [9]?

The issue of premature mortality in specific groups of individuals can be addressed by asking the question, "what allows some people to live longer than others?" This interesting question has been investigated through the study of centarians (people who live beyond age 100) and the close analysis of factors that such long-lived people share [10, 11].

The frequent observation that an important predictor of long life is being born to long-lived parents implicates inherited genes in longevity. Diet (low caloric intake), a life style that promotes heart heath, a solid support network of friends and family, and a subjective sense that life has a purpose are the factors other than longevity genes that studies of centarians have found to contribute to exceptionally long lives [12].

This paper will review the influence of four longevity factors (genes, diet, support network, and sense of purpose) in the lives of people with schizophrenia. The databases, PubMed and Google Scholar, were searched for studies, mainly those conducted over the last decade, which shed the most light on these influences (Fig. 1).

Findings

Longevity Genes

Between 15 and 40% (the percentages vary from study to study) of life expectancy is believed to be predetermined by the presence of specific gene variants [13, 14]. The research on long-lived populations has yielded approximately 77 candidate pro-longevity genes, chief among which are apolipoprotein E (APOE), forkhead box 03 (FOXOS), interleukin 6 (IL6), insulin-like growth factor-1 (IGF), chromosome 9P21, and 5q.33.3 [15, 16]. It is important to note that the full effect of one's genetic inheritance may not be felt until late in life when DNA "packaging" -e.g. epigenetic DNA methylation and histone modification tends to drop off. As cells age, chromatin marks drift towards a middle ground between repressed and active, such that genes that were previously inactive begin to "leak" [16]. The corollary is that, since most people with schizophrenia die relatively young, the major determinants of longevity in this population are likely not to reside primarily in genes but more in environmental conditions alone or in products of gene-environment interactions [17].

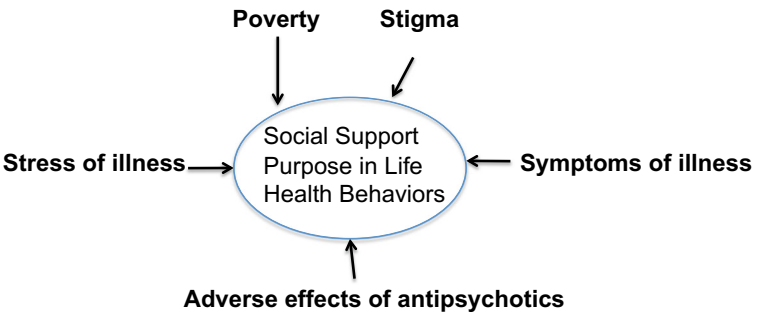

Fig. 1 Modifiable aspects of schizophrenia mortality

Gene/Environment Interactions

Hormones, diet and exposure to physical and psychological stressors are important environmental influences that interact with genes, most particularly during sensitive periods of development such as fetal life and early childhood. The results of such interactions affect health throughout the lifespan. Harmful exposures during these early periods are able to directly trigger ill health or they can do so indirectly by setting off chains of adverse events. For instance, subpar parental care may lead to poor quality or short duration of schooling, subsequently to unrewarding employment and low income, to poor housing, to insufficient levels of social support, and from that to unwise health behaviors that culminate in serious illness [18]. Chains of adverse effects may not be the only routes to ill health. What matters more may be the rate and accumulation of chance noxious exposures (accidents, toxins, infections, global economic conditions, wars, natural disasters), which each work through DNA methylation and histone modification and non-coding RNA to suppress protective genes or to enhance the expression of disease genes [19].

Exposure - Prenatal Environment

While harmful exposures can occur at any time, there is evidence that what happens early in life is especially critical to future health. Fetal programming is the name given to the link between the fetal environment and later life effects on the immune, endocrine, metabolic, cardiovascular, and central nervous systems [20, 21]. When an expectant mother experiences stress, the fetus is exposed to excess glucocorticoids via placental transfer. The fetoplacental barrier to maternal glucocorticoids is not robust; high cortisol levels enter the fetal bloodstream and often lead to low infant birth weight, which, in turn, increases the risk for a variety of adult illness such as coronary heart disease, stroke, type 2 diabetes mellitus, adiposity, the metabolic syndrome, and osteoporosis [22].

There are other mechanisms by which maternal stress during pregnancy can affect the adult health of offspring. For instance, maternal undernutrition during pregnancy promotes epigenetic changes in the expression of genes involved in endothelial function, thus facilitating vascular disease [23]. Another example is maternal hyperglycemia, which leads to fetal hyperinsulinemia and fat deposition, consequently increasing the risk for metabolic disorders in offspring in adulthood [24].

One reason why fetal exposures such as maternal nutrition, stress, toxic chemicals, drugs, or diseases are of particular importance is that epigenetic processes (the influence of the local environment on gene expression) in the placenta differ from these same processes in other tissues [25], which may make their effects more durable.

Exposure - Early Childhood

Early childhood is another sensitive period for epigenetic effects. Potential noxious exposures at this time are infections, accidents, toxins, parental neglect, physical, sexual, or psychological abuse, and inadequate nutrition. Young children can also be exposed to continuing adverse circumstances such as occur with chronic illness in the family or chronic economic disadvantage or war. A recent report suggests that early childhood trauma such as this is associated with dysregulation of the immune system in adulthood [26].

Exposure -Adolescence

Significant stressors often appear during adolescence – the advent of puberty and pressures related to family, school, accidents, illnesses, peer relationships, and exposure to toxic substances. It is during adolescence that young people begin to see themselves as occupying a more or less fixed rung in the social hierarchy. Such social positioning is crucial to self-esteem and becomes a major determinant of adult goals and aspirations. It is also during adolescence that sexual preferences are solidified and sexual intimacy becomes an important motivator of behavior.

Schizophrenia generally begins at this time. This may be because the threshold for the large number of genes that need to be "turned on" in order for the symptoms and signs of illness to emerge has now been reached.

Low Caloric Intake

The association of lean body mass with exceptional longevity is corroborated by many animal studies [27]. A study in monkeys has shown that reduction of food intake delays the risk of diabetes, cancer, cardiovascular disease, and brain atrophy [28]. Studies of long lived humans confirm that eating in moderation and eating mostly plant-based diets, goat's milk, red wine, and herbal teas in the context of adequate hydration, physical exercise, abstinence from alcohol and tobacco and maintenance of a low body mass index have been associated with longevity in humans. While reducing caloric intake extends life span, individuals with schizophrenia tend to eat a high calorie diet, high in saturated fat and low on fibre and fruit; their diet increases the risk of metabolic disease [29]. Although the high calorie diet found in schizophrenia has many explanations (substance use, medication-induced cravings, insufficient training in food preparation, general apathy, living in proximity to fast food outlets), the overall reason is probably socioeconomic disadvantage. Healthy diets cost more than unhealthy diets [30]. Foods of lower nutritional value generally cost less per calorie than nutritious food and fruit and vegetable stores are often not available in areas where the economically disadvantaged live. Low socioeconomic status, especially when coupled with low educational achievement, is known to be associated with a diet low in nutrients and high in calories [31, 32].

Social Networks

Social networks provide a) emotional support (comfort, belonging, understanding, reassurance), as well as b) informational support that assist decision-making with respect to symptoms, medication and health behaviors. They also provide c) physical support (physical comfort, nutrition, transportation) and d) practical support (financial, housekeeping), in addition to e) psychological support that augment a sense of personal control and self-esteem, and f) social support (relationships, community acceptance) and, finally, g) spiritual support - encouraging interrogation and discussion of the meaning and purpose of life [33].

Because people with schizophrenia frequently experience difficulties in developing and maintaining social relationships, they tend to have small social networks that are mainly composed of family members and care providers [34]. In a meta-synthesis of studies of the lived experience of individuals with schizophrenia [35], patients reported that their illness

affected existing relationships negatively, that the relatively few relationships that were retained tended to be superficial. This is not only because of a lack of social skills. Solitude is sometimes actively sought. It reduces unwelcome arousal and serves as a protective mechanism that is often purposefully resorted to by individuals with psychotic illness [36]. Communication and cognitive difficulties, lack of social motivation and the stigma that attaches to both mental illness and to social disadvantage further contribute to the social distancing and subsequent social isolation of individuals with schizophrenia [37].

From the viewpoint of living a long life, social withdrawal is a distinct disadvantage. Active engagement with social networks and support systems confer longevity benefits because close family and friends are necessary to mobilize resources as needed, to provide spurs to healthy behavior, to help access medical care in a timely fashion, and to supervise and reward the effective self-management of symptoms [38]. Being part of a social network encourages conformity to social norms with respect to health and self-care. In addition, being part of a social network endows its members with meaningful social roles that raise self-esteem and lend purpose to life [39]. A sense of purpose, as we shall see in the next section, is itself associated with longevity. Social connections also buffer the deleterious effects of stress. This may be mediated by a reduction in sedentary time and an increase in physical activity, as has been shown in elderly populations [40].

A review of 148 studies (308,849 participants) found a 50% increased likelihood of survival over controls for participants with strong social relationships. The influence of social relationships on risk for mortality was comparable to that of cigarette smoking and exerted a greater effect than obesity or alcohol abuse [41]. Moreover, a recent meta-analysis found that social disconnection was linked with a 29% increased risk for development of coronary heart disease and a 32% increased risk for stroke [42].

Altogether, an increased mortality risk of 29%–32% has been reported for socially disconnected adults in the general population [43, 44]. A 13-year follow up found that individuals with psychosis who lived alone were more often dead at the end of the study than those who smoked cigarettes or those who suffered from metabolic syndrome [45].

Purpose in Life

As mentioned earlier, a subjective sense of meaning and purpose in life is associated in the general population with both lessened morbidity and with longer life [46, 47]. This is a frequently reported association but could be explained by the fact that healthy people are more likely to seek and find a purpose in life than are those who are frail and disabled. Nevertheless, sensing a purpose to one's life has also been found to increase one's ability to counter stress and to lower allostatic load (neuroendocrine, cardiovascular, immune and metabolic burden) [48, 49].

In a study from China, more centarians reported viewing themselves as useful than did younger cohorts among the elderly [50]. Despite the fact that there are many ways to find meaning in life –being useful to others, immersing oneself in spirituality, in philosophy, in science or in art, for most people, meaning is found when belonging to a community of family and friends [51].

A sense of belonging is intimately tied to the feeling that life matters [52]. Social exclusion impairs a person's sense not only that life is worthwhile but also that one is in full control of one's life. Being in control rather than life being determined by chance or by others is thought

to prevent illness by reducing cortisol levels (a marker of stress) [53]. What is also likely is that individuals who are convinced that their life is significant pay careful attention to their health behaviors. They are more likely than others to abstain from cigarettes and alcohol, eat a healthier diet, engage in physical activity and participate in preventive programs – flu shots, daily aspirins and statins, cholesterol tests, colonoscopies, mammograms, pap smears, and prostate screening [54].

Having aspirations and pursuits and continually striving to attain goals provides life with meaning and purpose and enhances vitality. Unfortunately, those with severe mental illness are barred by symptoms, economic disadvantage, and perceived stigma from occupational activities that provide purposeful goals [55]. Many, instead, find purpose in active engagement in leisure activities [56]. For those with chronic illness, or for those living under economic constraints or for everyone as they grow older, leisure time activities become significant [57–60]. Even everyday activities can become imbued with meaning [61, 62], especially if they afford an opportunity to overcome challenges, learn new skills or help others [63–65].

Although taking care of other people can be both burdensome and stressful, it can also lend importance to life [66]. Many studies have confirmed that family caregivers have lower mortality rates than non-caregivers, although this may not hold across all samples of caregivers [67].

Individuals with schizophrenia do not often have the opportunity to care for others nor can they usually take part in leisure activities that are costly, such as those that involve travel or membership fees or supplies they cannot afford. Many, however, do find purpose in the arts and in religion [68, 69].

Discussion

The genes we are born with and the early exposures that negatively interact with our genes are random events over which we have little control. There is some measure of control, however, over other predictors of longevity -e.g. diet, social engagement and finding meaning in life, but economic constraints govern all three. The economic disadvantage that is tied to serious mental illness, as a consequence, plays a critical role in shortening the life of individuals with schizophrenia.

Persons with severe mental illness usually live in poverty [70]. Poverty determines where people live, what they eat, who their friends are, how they spend their time and what they do to keep healthy [71]. Poverty determines people's attitudes towards health, the extent of their exposures to health threats, their risk behaviors, and their interactions with health providers. Poverty also governs their relative ease of access to medical care. The difficulties inherent in living in deprived economic circumstances, compounded by the stress, isolation and the stigma of poverty, are well-known barriers to timely and effective illness prevention and healthcare [72]. It is seldom possible when researching mortality risks to disentangle the role of poverty from that of illness, its treatment, and its various sequelae.

To study the effects of socioeconomics on mortality rates, Davey Smith et al. conducted an ingenious study in Glasgow, Scotland in 1992 [73]. They took advantage of the observation that Glasgow graves between 1801 and 1920 were marked with commemorative obelisks of uniform design but of different heights. The taller the obelisk, the greater it cost so that the height of the obelisk made a good proxy for the financial means of the grave occupant. Since birth and death date were indicated on the

gravestone, Davey Smith and his colleagues were able to show that the higher the obelisk, the longer the person had lived. In 2000, Gould and Chappel [74] conducted a similar study in England by measuring the depth of burial of the dead body (the deeper the grave, in this case, the more it had cost). The age of death rose with increasing depth, again demonstrating a socioeconomic gradient in a particularly memorable way.

The stress that is linked to serious mental illness also plays a major role in schizophrenia mortality. Stress can come from both physiological sources -e.g. pain or hunger, and from psychological sources -e.g. social evaluation, social exclusion, or social competition [75]. Experiencing stress leads to a state of arousal that is accompanied by heightened cortisol, epinephrine and norepinephrine secretion, all of which results in a rapid heart rate, endothelial dysfunction and tissue inflammation that raise blood pressure. This varies with the intensity and the nature of the stressor as well as with the person. In general, however, cumulative stress is an important risk factor in early mortality [76, 77].

Cumulative physical stress in schizophrenia, assessed by 13 biological markers in cardiovascular, metabolic, neurendocrine, and immune systems, has been found to be significantly higher than in age peers [78]. These markers are already pathological in early disease [79] and in medication-free patients. They improve with antipsychotic treatment [80].

The very symptoms of schizophrenia –e.g. apathy, social withdrawal, cognitive problems, hostility, fear and suspicion, contribute to poor health and early mortality. Cognitive deficits make it difficult to accurately interpret the significance of medical symptoms and to appreciate behavioral risks. Motivational problems interfere with participation in preventive screening; fear and suspiciousness undermine trust in medical care [81]. Symptoms may contribute to a high rate of accidents and injuries. Also prevalent are suicidal thoughts. Suicide is 7 times as common in schizophrenia as in the general population [2].

Mental illness stigma has public health implications [82]. Not only is it a source of stress but it also interferes with timely access to services and to cutting edge treatment and quality care. It also leads to self-stigma, and loss of confidence, which consequently makes it hard for people with schizophrenia to speak up for what they need from health providers. Their tendency is to avoid people in authority. Unconscious mental illness stigma influences the medical profession as well. When faced with a patient diagnosed with schizophrenia, doctors sometimes do not take physical symptoms seriously, attributing them to the delusions of mental illness [83, 84]. In general, medical staff tend to systematically treat the physical illnesses of people with mental illness less thoroughly and less effectively than they do those they consider mentally well [1].

The day-to-day life of people with schizophrenia is often marked by sedentariness, loneliness, substance use, including cigarettes, alcohol, marijuana, and an unhealthy diet. Their life style has been held responsible for poor health and early death [2]. They are frequently the targets of violence. Death by suicide, homicide and accident together account for approximately one in every eight schizophrenia deaths [85], accidental death being twice as prevalent as suicide [2].

A critical issue is the extent to which treatment with antipsychotic drugs contributes to ill health. Antipsychotics result in weight gain and lipid and glucose dysregulation [86]. Antipsychotics may add to memory impairment, with subsequent risk-taking and accidents, lack of hygiene and inadequate self-care, perhaps explaining the high rates of infectious disease. Antipsychotics are also implicated time wise because the mortality gap between schizophrenia and the rest of the population is widening since the introduction of 2nd generation weight-inducing antipsychotic drugs [87, 88]. On the other hand, antipsychotics lower the suicide rate, reduce psychotic symptoms, and can be expected to increase social support and decrease

distrust of medical intervention, perhaps explaining why markers of disease are decreased in individuals with schizophrenia after treatment [80]. Recent papers appear to exonerate antipsychotics as the cause of the high death rate in schizophrenia. The meta-analysis by Carpiniello et al. [5] strongly suggests that individuals with schizophrenia who are taking antipsychotics have a lower overall mortality rate than those not taking antipsychotics. The important question is whether the long-term use of antipsychotic medication, especially at high doses, hastens cardiovascular deaths by cumulative exposure to cardiometabolic side effects [89]. Doses and durations of exposure need to be examined. While there has been a 40% drop in death rate due to suicide in schizophrenia, from 16.2% of deaths in 1984 to 4.0% of deaths in 2014 [90], cardiovascular deaths continue to rise [91, 92].

Conclusion

Currently, individuals with schizophrenia die, on average, 20 years before their peers, with 80% of deaths resulting from 'natural' causes, mainly cardiovascular. The aim of this paper was to review this premature mortality from the perspective of factors known to be shared by centarians, to see whether these factors were deficient in schizophrenia. Findings were that individuals with schizophrenia generally lacked three crucial longevity factors: life behaviors that promoted heart health, sufficient social support, and a belief in a purpose to their life. These factors are potentially modifiable but there are strong barriers to change, namely poverty, symptoms specific to schizophrenia, stress, stigma, and adverse effects of antipsychotic medication. These must be addressed before effective change can take place in the duration of life in this population.

Compliance with Ethical Standards

Conflict of Interest The author declares that she has no conflict of interest.

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