Perspective

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The idea of uniform change: is it time to revisit a central tenet of Rose's "Strategy of Preventive Medicine"?[1]

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ABSTRACT

A mean-centric view of populations, whereby a change in the mean of a health variable at the population level is assumed to result in uniform change across the distribution, is a core component of Geoffrey Rose's concept of the "population strategy" to disease prevention. This idea also has a critical role in Rose's observation that individuals who are considered abnormal or sick (the rightward tail of the distribution) and those who are considered normal (the center) are very closely related, and that true preventive medicine must focus on shifting the normal or average. In this Perspective, we revisit these core tenets of Rose's concept of preventive medicine after providing an overview of the key concepts that he developed. We examine whether these assumptions apply to population changes in body mass index (BMI) and show that there is considerable evidence of a widening of the BMI distribution in populations over time. We argue that, with respect to BMI, the idea of using statistical measures of a population solely on the basis of means and the assumption that populations are coherent entities that change uniformly over time may not fully capture the true nature of changes in the population. These issues have important implications for how we assess and interpret the health of populations over time with implications for the balance between universal and targeted strategies aimed at improving health. *Am J Clin Nutr* 2016;104:1497–507.

Keywords: sick populations, Geoffrey Rose, high risk, population strategy, uniform change, dispersion, inter-individual inequality

INTRODUCTION

Geoffrey Rose's seminal concepts of disease, public health, and prevention, which were introduced >3 decades ago, are foundational to the fields of epidemiology and public health (1, 2). Rose's ideas (2) were remarkable for their breadth, covering theories from disease causation to the consideration of the ethics of treatment and prevention, which made a compelling case for a population-centric approach to disease prevention. A core tenet of Rose's concept of preventive medicine (2) was his assumption that, across a range of biologic measures (e.g., blood pressure or blood cholesterol), the width of the distribution of these measures remained relatively similar across different populations even as the mean of the distribution shifted. This idea of uniform change across a distribution as the center shifts, and the preserved distance between the tails of distribution (i.e., a mean-centric view of population), has considerable statistical and conceptual implications. Statistically it implied that the central tendency, or mean of the distribution, could be used as a proxy measure of a population's intrinsic traits, an idea that resonates with Adolphe Quetelet's 19th century notion of "l'homme moyen" or the average man (3–5). Approaching 2 centuries later, the use of mean risk factors to track population trends has become an integral and seldom-questioned part of scientific assessments and public health–policy narratives (6–9). For Rose, a related conceptual implication that the position of the population mean was closely tied to the position of the distributional tails had profound importance (10). He argued that in each population, there is a link between those considered "abnormal" or sick (the rightward tail of the distribution) and those considered "normal" (the center), and that true preventive medicine must focus on shifting the "normal" in society.

In this Perspective, we revisit the concept of the uniform change in the population distribution of risk factors developed and applied by Rose in his articles (11–13) and in his text *The Strategy of Preventive Medicine* (2). We examine whether this concept applies to changes in the distribution of BMI across multiple populations and within populations over time. This Perspective is structured in 3 parts. First, we examine the idea of a continuum between normalcy and deviance. Rose illustrated

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this idea using examples such as blood pressure and LDL cholesterol, risk factors that have a monotonic association with risk, with higher levels implying greater risks (14, 15). We discuss Rose's concept of prevention in the context of evidence supporting a potentially U-shaped relation of BMI to risk that is plausible in low-income countries (16, 17). Second, we review the concept and historical antecedent of Rose's ideas of a sick population, sick individuals, and the population strategy to disease prevention (2). Third, in light of an emerging body of evidence suggesting a widening of the BMI distribution in populations over time (15, 18–28), we examine the impact of this phenomenon on Rose's concept of preventive medicine and consider the implications for health inequality of widening distributions.

THE CONCEPT OF A CONTINUUM BETWEEN NORMAL AND DEVIANT

In clinical practice and public health, continuous measures are often dichotomized to make treatment decisions or to track "disease" burdens in populations. In arguing against artificial boundaries between the normal and the deviant, Rose built on a long tradition which in the context of modern social medicine can be traced back to John Ryle (29). Rose recognized that the individual-centric approach to both clinical medicine (identifying and treating illness) and public health (preventing people from becoming sick) had led to a dichotomization of individuals into sometimes unhelpful classes of normal and sick (11). For example, clinicians need to know when to initiate the treatment of hypertension, and public health officials need case definitions to quantify an outbreak of *Salmonella*. The need to classify is widespread, and as a consequence, artificial lines are introduced, obscuring the underlying continuum. As Rose stated (11, p. 1405),

> This dichotomous thinking carries over into many areas. We speak of a risk factor as being present or absent, and we count the number of risk factors that a patient possesses. We say that a patient either has coronary heart disease or is free of it. We speak of 2- or 3-vessel coronary disease as though coronary artery narrowing is either present or absent. We say that an effect is either statistically significant or non-significant. In all of these ways, we prefer to recognize only black and white because shades of gray introduce confusion and uncertainty. We prefer to suppose that normalcy and deviance can be clearly separated because that confines our worries to a defined minority of deviants: Most people are all right, really!

In reality, many entities in medicine and public health exist along a continuum without an intrinsic or naturally occurring cutoff that distinguishes the sick (or "deviant" according to Rose's terminology) from the normal. In recognizing this fact, Rose drew on George Pickering's insight that blood pressure values in a population form a single distribution (rather than separate distributions of "hypertensives" and "normotensives"), and that the line that distinguishes normal from hypertensive was arbitrary (30). Rose described Pickering's influence (11, p. 1405):

> In 1954, I was working as a physician for my teacher and father in medicine, George Pickering. In that year, he published his articles on the nature of hypertension, in which he introduced the revolutionary notions that the diagnosis of hypertension is a man-made artifact; that the distribution of blood pressure is continuous, with normalcy merging imperceptibly into deviance; and that hypertension is thus not a naturally defined entity.

Sixty years later, the elusive goal of trying to identify the "best" threshold for initiating treatment remains a focus of much clinical research, triggering a new generation of large multisite clinical trials (31). For example, the recently completed Systolic Blood Pressure Intervention Trial argues for a marked lowering of treatment thresholds for hypertension from the long-standing systolic blood pressure threshold of 140 to 120 mm Hg, once again attempting to redefine the line between normal and deviant (31).

It should be noted that Rose's argument for a continuum between normal and deviant in the case of blood pressure has been strongly supported by scientific advances over the subsequent 4 decades. Rather than a small number of genes being responsible for elevated blood pressure, many genes can contribute to elevated blood pressure, with the effect of each being small, $\sim$<0.5 mm Hg diastolic (32). However, it is also possible that the tail of the distribution and the center may not share common determinants (33). For example, for measures of human intelligence such as the intelligence quotient, the majority of the population varies continuously through the impact of multiple, widely shared, but small effect-size environmental and genetic influences. However, isolated effects, such as a single point mutation or a severe environmental insult (e.g., perinatal hypoxia), can predict severe intellectual disability (33–35).

Similar to blood pressure (15), other risk factors have a monotonic relation with disease risk, with no clear lower threshold for risk—for example, the relation of cholesterol to heart disease (14). Rose argued that this continuous relation could result in the majority of cases of disease in a population arising in individuals who would be below the threshold of "high risk" for an exposure. Using cholesterol and the definition of high cholesterol at the time, 90% of heart-disease cases arise in the segment of the population who are considered to have "normal" cholesterol (**Figure 1**). This occurs because even small rises in cholesterol, which are well within the average range of Western populations, are associated with increased risk, and the

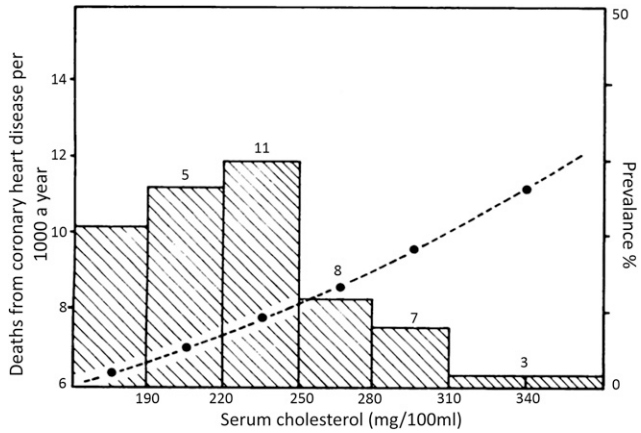

FIGURE 1 "Prevalence distribution of serum cholesterol concentration related to coronary heart disease mortality (----) in men aged 55-64. Number above each bar represents estimate of attributable deaths per 1000 population per 10 years. (Based on Framingham Study)." Reproduced from reference 13 with permission.

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impact of this risk across a large segment of the population could generate large numbers of cases. Rose stated (11, p. 1406),

> The large majority of coronary deaths do not occur in the high-risk sector that would be picked out for medical care but rather in the far larger number of people with average levels of risk factors. Prognostically speaking, average cholesterol is high cholesterol, average blood pressure is hypertension, and average weight is obesity. It is not just the deviant minority of people who have a problem.

This emphasis on the continuum of risk underscored the importance of studying the entire distribution of a risk factor and the key importance of the central tendency of the distribution within a population.

ROSE'S CONCEPT OF A POPULATION STRATEGY FOR PUBLIC HEALTH

In this section, we summarize Rose's "population strategy" for public health. He advanced a rationale for the focus on populations (as opposed to individuals), which led to an elaboration of the notion of "sick populations."

Population focus: the rationale

Building on the work of Ancel Keys in the landmark Seven Countries Study (36), Rose conceptualized each country's population as a coherent whole. This idea of a population, as determined on geographic and statistical grounds, drew on a long historical tradition (**Appendix A**). Rose described Keys's influence (11, p. 1405):

> It was Ancel Keys who led us to confront the more fundamental question, namely, why did the western epidemic of heart disease occur in the first place? Why do population incidence rates vary? … he also taught us to investigate the problems of a mass disease from a new viewpoint—that of the sick population.

When examining the relation between aggregate national dietary variables and 15-y mortality in the Seven Countries Study, Keys noted how a careful interpretation of these population-level associations might play an important complimentary role to individual level analyses (37, p. 904), stating, "…such strong relationships between death rates and specified characteristics of the populations cannot be ignored. It is urged that evaluation of risk associated with specified variables should consider the relative risks found in comparisons of populations as well as the risks of the individuals within those populations."

Keys also felt that population-level measures (essentially individual-level health or behavioral data aggregated to a mean at the population level) were of particular value given their relatively low variance relative to individual variation (38). Again, using the example of dietary measures, he stated (38, p. 904),

> The approach using the averages for the nutrients in the diets of population samples was forced by consideration of the extreme limitations of dietary estimates for individuals. Repetitions of dietary surveys on the same free-living men consistently show that the intra-individual variance tends to be of the same order of magnitude as the inter-individual variance… On the other hand, it is possible to characterize the average diet of a population by repeated dietary surveys…on statistically selected subsamples of the population.

Keys's argument for population measures having relatively low variance compared with individual measures, and the value of focusing on the population, was carried forward by Rose, who contended that in many circumstances it was hopeless to even try and explain individual risk (12, p. 429):

> Within populations it has proved almost impossible to demonstrate any relation between an individual's diet and his serum cholesterol level; and the same applies to the relation of individual diet to blood pressure and to overweight. But at the level of populations it is a different story: it has proved easy to show strong associations between population mean values for saturated fat intake versus serum cholesterol level and coronary heart disease incidence, sodium intake versus blood pressure, or energy intake versus overweight. The determinants of incidence are not necessarily the same as the causes of cases.

The challenge of obtaining precise data at the level of the individual continues to plague epidemiologic studies, further supporting Rose's focus on population-level risk factors. For example, a recent review of the validity of dietary estimates of caloric intake in the NHANES suggests that there have been severe data-quality limitations that have shown only marginal improvements through 4 decades of progressive survey cycles (39). More broadly, the limitations of trying to explain individual variations, especially when they might reflect fundamental stochastic processes, need to be recognized (40). At the same time, some biologic phenomena demonstrate individual variation not captured by patterns at the group level. For example, brain-activation patterns in episodic retrieval show reliable and distinct patterns at the individual level not captured at the group level with implications for how we understand the role of the brain architecture in the retrieval process (41).

The concept of sick populations

Keys's articulation of the need to focus on the population in addition to the individual formed the very core of Rose's concept of preventive medicine (11). In an often-reproduced figure from the Seven Countries Study that compared the cholesterol distribution in Finland and Japan, Rose discussed the idea of sick populations (**Figure 2**). Within both populations there were individuals with relatively high cholesterol, but what was perhaps most notable was the difference in the mode of the 2 distributions, with Finland shifted far to the right of Japan, so that the majority of individuals with "low" cholesterol in Finland (relative to the norm in Finland) would have been considered to have high cholesterol (relative to the norm) in Japan. With respect to cholesterol or cardiovascular disease risk, Finland could be considered a "sick population," and Rose argued that the most efficient method of improving the health of sick populations was through changing the "normal," in short, through change in society itself (12, p. 430):

> If non-smoking eventually becomes "normal", then it will be much less necessary to keep on persuading individuals. Once a social norm of behaviour has become accepted and (in the case of diet) once the supply industries have adapted themselves to the new pattern, then the maintenance of that situation no longer requires effort from individuals. The health education phase aimed at changing individuals is, we hope, a temporary necessity, pending changes in the norms of what is socially acceptable.

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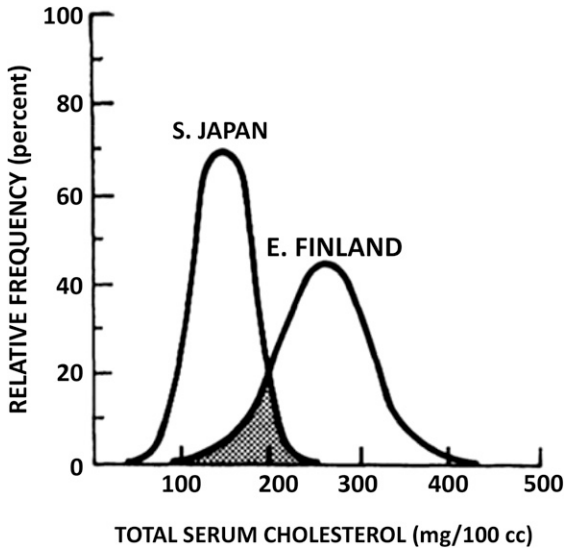

FIGURE 2 "Distribution curves of serum cholesterol levels in South Japan and East Finland from Keys's Seven Countries Study." The shaded region represents the overlap between the 2 population distributions. Reproduced from reference 11 with permission.

The population strategy

The population strategy to disease prevention relies on the continuum between normal and deviant, the monotonic rise in risk associated with elevations in risk factors such as cholesterol, and the observation that population distributions of an exposure can be shifted (e.g., toward Japan, compared with Finland). Using Rose's assumption of a fixed distributional width, the shifting of a population could be represented statistically by changing only the central tendency of that population, i.e., the mean. When describing the fundamental underpinning of the population strategy, Rose, adopting the vision of Keys, stated (12, p. 431), "The Population Strategy – This is the attempt to control the determinants of incidence, to lower the mean level of risk factors, to shift the whole distribution of exposure in a favorable direction."

The population strategy, if adopted, would have many implications for how we implement prevention and treatment given the traditional focus by the health care system on the deviants of the population distribution, i.e., the "high-risk" tail. The population strategy changes the "normal" in social and cultural contexts in which "lay epidemiology," which is the understanding of health risk and disease by the general public, already plays a prominent role in the understanding of causes of disease and affects the public uptake of health-promotion messaging (42). In Rose's concept (2) of how the population strategy would be implemented, there is an explicit assumption that, in its most desired and efficient form, it would encompass broad changes in social, economic, and political structure—the "mass solutions"—rather than be driven by an individualizing approach of medicalization and pharmacotherapy, applying the conventional biomedical model. Here, Rose was clearly influenced by findings regarding pharmacologic cholesterol lowering with the evidence in randomized controlled trials at the time he was writing suggesting possible unfavorable effects (43). He wrote (12, p. 432):

> In mass prevention each individual has usually only a small expectation of benefit, and this small benefit can easily be outweighed by a small risk. This happened in the World Health Organization clofibrate trial, where a cholesterol-lowering drug seems to have killed more than it saved, even though the fatal complication rate was only about 1/1000/year. Such low-order risks, which can be vitally important to the balance sheet of mass preventive plans, may be hard or impossible to detect. This makes it important to distinguish two approaches. The first is the restoration of biological normality by the removal of an abnormal exposure (e.g. stopping smoking, controlling air pollution, moderating some of our recently-acquired dietary deviations); here there can be some presumption of safety. This is not true for the other kind of preventive approach, which leaves intact the underlying causes of incidence and seeks instead to interpose some new, supposedly protective intervention….

The example of the clofibrate trial was repeatedly raised in Rose's writings and understandably seems to have had a considerable influence on his thinking. Contrasting cholesterol-lowering drug treatment with a population strategy of reduction in salt intake, he wrote (2, p. 146):

> To take a contrasting example, the situation with regard to the potent cholesterol-lowering drugs is quite different. Experience with their predecessors warns us that unforeseen adverse effects may occur, and that these can only be identified and measured by large long-term controlled trials. It will be many years before even medium-sized trials have been completed, and no current trial has adequate power to identify important but delayed adverse effects. The drugs represent a major pharmaceutical advance, but their widespread promotion and use, outside high-risk groups is quite wrong. The over-use of drugs is a constant danger in preventive medicine and a near-inevitable consequence of mass screening.

Rose (2) further emphasized this contrast (with italics retained; p. 80–81), stating,

> The lesson from this trial is important: *the long-term of use of drugs in prevention is justified only within a high-risk group.* We have no means of excluding a level of risk which, however small for the individual, might exceed the hoped for benefit—except where that benefit is known to be substantial. This effectively rules out any mass use of long-term drugs, especially since trials rarely continue for longer than about 5 years, leaving us quite in the dark concerning lifetime effects. It is only in individuals known to be at exceptional risk that such uncertainty may be acceptable.

From this example, much of general importance was abstracted, and thus the change in evidence with respect to the use of long-term cholesterol lowering with considerably more effective agents, in particular statins (44), should influence how the case is framed today. For example, 1 in 5 individuals aged 40–75 y in the United Stated is currently taking a statin (45); if populations at risk of myocardial infarction are examined, one-third of individuals are already taking a statin at the time of their first myocardial infarction (46), and if the new American College of Cardiology and the American Heart Association guidelines were applied, ~1 in 2 adults in the United States would be eligible for a statin (45). These data show the remarkable rise in the use of pharmacologic therapy for primary prevention in the 2 decades since the landmark Scandinavian Simvastatin Survival Study trial (47), a trial that was published 1 y after Rose's death, providing the first robust evidence supporting the use of a cholesterol-lowering drug that could have broad application. When comparing statins to clofibrate, the markedly better benefit-to-risk profile of statins (and even the reported adverse effects of statins are likely overstated) (48) has blurred the lines between the relative merits of the population approach over the

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high-risk strategy (49). Co-opting the traditional territory of public health, the medical profession has shifted much of its focus toward prevention through the use of medications on a mass scale, with the number needed to treat (i.e., the number of individuals needed to be treated with an agent to prevent 1 clinical event in a defined time interval) for the primary prevention of cardiovascular disease being >100 for a statin taken over a 5-y interval and >1000 in the case of aspirin over a 1-y interval (50, 51). Rose's argument for demedicalization through the population strategy to disease prevention has now morphed into a situation in which the division between population-level prevention and medicalization has become blurred.

CENTRALITY OF UNIFORM CHANGE TO THE POPULATION STRATEGY

At the heart of Rose's conception of the population strategy to disease prevention, and key to the idea of the coherent nature of populations, was the observation that most risk-factor distributions across populations—and within populations over time—appear to have uniform displacements, with risk changing the same amount at different parts of the risk-factor distributions (**Figure 3**). Using blood pressure levels from the InterSalt study as an example, Rose described how an assumption of constant dispersion (i.e., uniform change) anchors his population strategy (52, p. 411–2):

> The population or public health approach starts from the observation that when different populations are compared, we see a shifting of the whole distribution. Within each population the spread between the two extremes is rather similar…If we want to know why one population has more hypertensives, then research into the peculiarities of the affected individuals will not tell us: rather we need to look for those factors which influence the population as a whole…This is the basis of the population or public health approach.

Rose placed great value in the role of mean risk-factor levels in capturing something intrinsic and essential about a population's normative tendencies, in part because of the strong statistical relation he observed between the mean and deviance. Across a range of behavioral, dietary, and biologic measures in the InterSalt study, he demonstrated that mean levels of a risk factor were tightly correlated to the prevalence of deviance, an argument for the interconnectedness of populations and the idea that what is normal creates a permissive environment for what is deviant (**Figure 4**) (10). Toward the end of his career, Rose became increasingly interested in psychological factors as well as behavioral (e.g., alcohol drinking) and physiologic risk factors for chronic disease (53). He saw psychiatric illness as the tail of a distribution of psychological state, and he surely would have appreciated the application of his ideas to issues such as problem gambling, in which changes in the level of population gambling related to increases in population average gambling after the introduction of a national lottery (54).

Rose (2) noted that the uniform change assumption may not be applicable to BMI (**Figure 5**), and for other measures such as blood pressure with aging, but did not, to our knowledge, offer a complete explanation as to how this issue should influence the broader idea of the population strategy. He also outlined the need to move beyond cross-sectional data to verify the uniform change model of population change (10, p. 1033):

> The distribution of each of these variables moves up or down as a coherent whole…the tail belongs to the body, and the deviants are a part of the population. The results show this to be a geographically worldwide phenomenon. It is hard to see how it could fail also to apply to temporal changes within a population…This, however, requires confirmation.

IS THE DISTINCTION BETWEEN THE HIGH-RISK STRATEGY AND POPULATION STRATEGY HELPUL? THE CASE OF BMI

Much has been written about the relative merits of the population strategy compared with the high-risk strategy (2, 55–60). The phenomenon of increasing dispersion in BMI presents unique challenges to this dichotomy and to the rationale for each approach. Two critical findings must be considered. First, an emerging body of evidence suggests that, from low- to high-income countries, the rise in mean BMI has not been accompanied by a uniform shift in the BMI distribution (i.e., the weights of populations have not changed uniformly) (18–26, 61–63).

Consider the situation in low- and middle-income countries where rising mean BMI was accompanied by increasing dispersion such that overweight and obesity rose at 60% and 40% greater rates, respectively, than the decline in underweight (22, 27). In high-income countries, dispersion has also increased. In

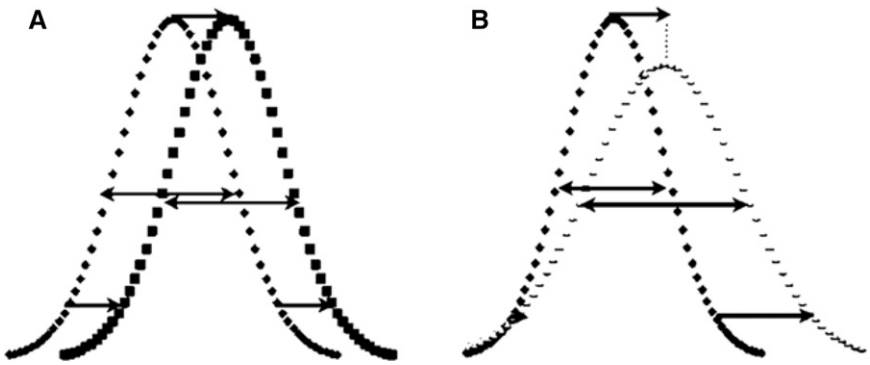

FIGURE 3 Comparison of 2 patterns of change of a theoretical risk-factor distribution from time 1 (diamonds) to time 2 (squares or dashes). (A) In a uniform-change model, all segments of the population show a similar increase over time, and dispersion is preserved (double-headed arrow). (B) In a situation in which increasing dispersion is occurring, higher segments of the distribution show a greater increase over time. Both scenarios A and B would have the same mean or average change.

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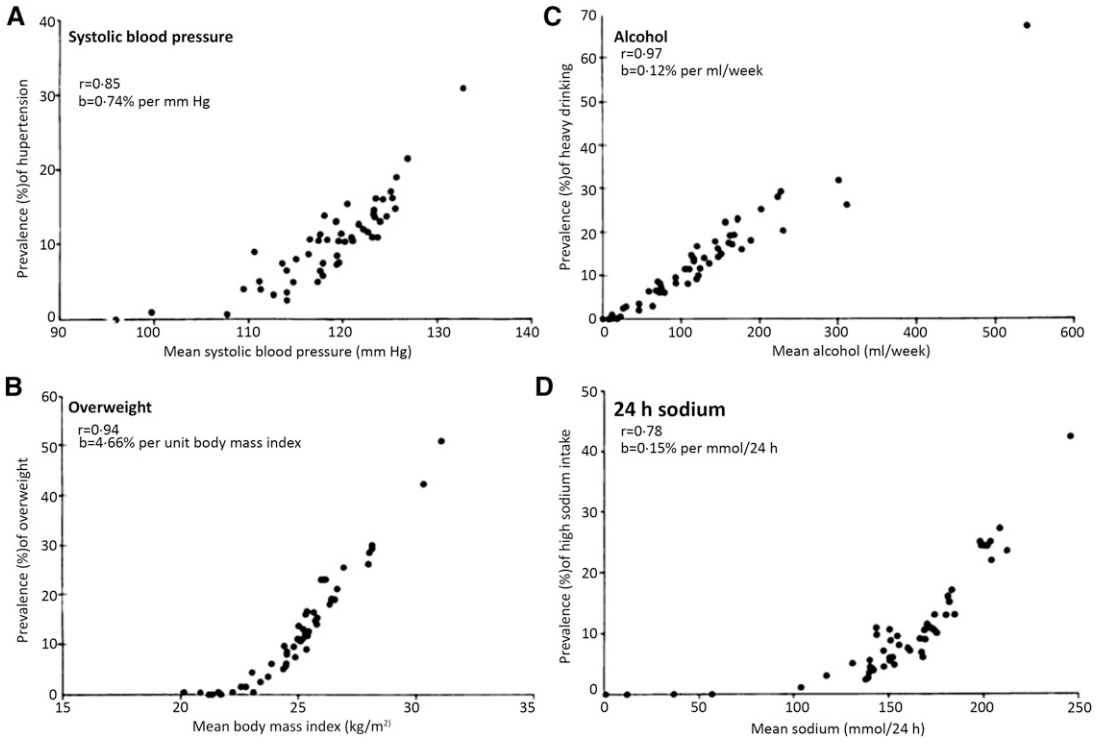

FIGURE 4 "Relation between population mean and the prevalence of deviant (high) values across 52 population samples from 32 countries (men and women aged 20-59); (A) systolic blood pressure, (B) body mass index, (C) alcohol intake, (D) urinary 24 hour sodium excretion." Reproduced from reference 10 with permission.

a recent article that used repeated cross-sectional data from the Behavioral Risk Factor Surveillance System sample on 25–64-y-old men and women from 1993 to 2012 in the United States, a >30% rise in dispersion (standard deviation) in BMI was observed, and this increase occurred consistently within different demographic and socioeconomic groups (21). Rising dispersion can also be quantified by the growing distance between the tails of the BMI distribution—this can be quantified by looking at the ratio of the increase in BMI at the 95th percentile compared with the fifth percentile. Across 37 low- and middle-income countries, the 95th percentile rose at 2.5 times the rate of the fifth percentile (22), and the ratio of 95th to fifth percentiles increased >17-fold in the United States (21).

There also seems to be the possibility that the distribution of BMI and the rightward tail of obesity may have distinct determinants. For example, although most germline genetic variants that have been identified and investigated in this light appear to contribute to increased BMI across the population spectrum (64, 65), new work in murine models raises the intriguing possibility of epigenetic changes creating a bimodal pattern of weight gain rather than a continuum, and parallel findings may exist in humans (66), although substantially more research is required to support this claim.

Rising dispersion in BMI questions the cohesiveness of populations and suggests that means or other aggregated ways of quantifying central tendency are not adequate on their own or when accompanied by simple dispersion measures such as standard deviation. Rising dispersion also potentially reduces the adequacy of statistical and etiologic models that are focused on predicting population-level differences in mean risk factors, the level of analysis advocated by Rose, Keys, and many public-health practitioners (12, 37). With the rapid rise in the variance in BMI within populations (22, 27), between-population differences in mean BMI may convey less valuable information.

While considering this phenomenon of rising dispersion, a re-examination of Figure 2 shows that, rather than a simple rightward shift of the distribution of cholesterol in Finland compared with in Japan, a substantial widening of the distribution of cholesterol in Finland can also be observed (as manifested by the relatively small distance between the leftward tail of the 2 distributions relative to the distance between the rightward tails, and the overall flattening of the curve). Similar to population

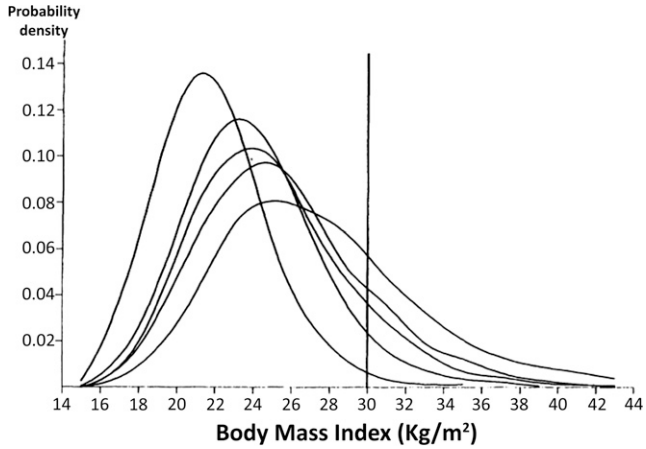

FIGURE 5 "Distribution plots of body mass index in five aggregated populations of men and women 20-59 years old grouped according to increasing levels of average body mass index." Reproduced from reference 11 with permission.

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transitions in BMI, this outcome raises the question of whether Finland truly had a coherent "sick population" in Rose's famous example, rather than the emergence of multiple overlapping subpopulations with distinct needs.

The second issue is the shape of BMI's exposure risk curve. The relation of BMI to mortality and morbidity may not follow a simple monotonic relation, and increased risk may occur in both individuals with very high and those with very low BMI (16, 61, 62). The relation of BMI to mortality has been described as J- or U-shaped (17, 67), with increased risk in individuals with very low weight that is plausible in low-income settings where a substantial burden of undernutrition continues to exist (16, 68). It should be noted that in high-income countries, the evidence for low BMI having a causal relation with mortality rests on far weaker evidence, with potentially substantial confounding between low BMI and smoking or premorbid illness (61, 69) and instrumental variable techniques greatly attenuating the low BMI-mortality association (70).

Rose (2) described different potential forms of exposure-risk relation, including the U-shaped form that BMI follows. However, his discussion of the tradeoff between the population strategy and high-risk strategy to disease prevention was mainly developed around monotonic exposure-outcome examples such as cholesterol and heart disease. In these situations, left-shifting the population distribution of exposure could reduce risk for all members of the population without appreciable harm for anyone, and the shape of the distribution seemed to be well preserved as the means shifted. For BMI, the fact that low and high BMI may correspond to increased risk, and the widening dispersion in the distribution, compel us to reframe how we think about the balance between the population strategy and high-risk strategy, especially in low-income settings. Rose acknowledged the limitation of the population-wide approach in these situations (2, p. 139–40):

> The population-wide approach seeks to move the whole distribution of a risk factor, including its low tail, in a favourable direction. Some individuals will stand to benefit much more than others, although ideally everyone would hope to gain something (for example, by…control of hazardous environmental pollution). This ideal will not be achieved if the curve relating exposure to risk is not linear, and especially if it is U- or J-shaped... It is possible that a reduction in alcohol intake might remove a protective factor against heart attacks, and when bad housing is demolished, long-time residents suffer an upheaval in their lives. In any widespread change some people will be hurt.

Consider again the situation in India, where a high burden of underweight and overweight or obesity coexist (22, 27). Increased risk at both very low and very high BMI indicates that a simple left shift of the distribution that may benefit the overweight or obese may further harm the underweight. Similarly, a right shift that benefits the underweight could potentially harm individuals with already-high BMI. In this scenario, a single population intervention (to address either underweight or overweight or obesity) would be hard to conceive when multiple "high-risk" and opposing interventions addressing the unique needs of each group are merited. The rise in dispersion and the disparate needs of each group undercut the very basis of describing them as being members of the same population (3), and simply shifting the population distribution would have less value than reducing dispersion. Meanwhile, in the United States, rising dispersion has led to a situation in which both a population strategy and a high-risk strategy have important public health roles. A population strategy to address obesity may have benefit for the majority of the population, given that more than three-quarters of adults between the ages of 20 and 60 y are overweight or obese (71). Of note, the benefits of weight loss may not extend to population segments such as the elderly or people in the normal weight range (61). Along with the population strategy, strategies targeted at high-risk groups with extremely elevated BMI are also important, when effective treatments are available. Recent evidence suggesting an improvement in long-term survival in individuals with grade III obesity [BMI (in kg/m^2) $\geq$40.0] who undergo bariatric surgery is one example (72). This group constitutes 6% of the adult population and suffers from markedly elevated comorbidity and overall mortality compared with those of average individuals with BMI of 28.7 (61, 71).

CONSIDERATIONS OF HEALTH EQUITY

Another important reason to not view the population strategy and high-risk strategy as a dichotomy in an era of rising dispersion is if we consider health inequality, which is defined as a measure of variation in a health metric across a population, in addition to social-group health differences, which are defined as mean differences in a health metric across subgroups designated by socioeconomic group or demographic characteristics (73). The idea of health inequality is especially relevant given the finding in the United States that the dispersion in BMI increased within different demographic and socioeconomic groups (21). Although population-wide approaches to health promotion could reduce both health inequality and group inequalities in health (59, 74, 75), they also have been observed to potentially increase health inequality, widening dispersion and accentuating differences between individuals with the best health characteristics and those with the worst (60). For example, a breastfeeding-promoting intervention was shown to widen socioeconomic disparities in exclusive breastfeeding rates at 12 mo (76), and population-wide approaches to increase folate intake in reproductive-age women may have widened socioeconomic disparities in folate use, especially when an agentic approach (i.e., public-knowledge campaigns that require individual agency to be effective) compared with a structural approach (i.e., food fortification) was taken (77). From a distributional perspective, these interventions would increase the mean of the outcome being measured (e.g., mean breast-milk consumption or mean red blood cell folate concentration) but would also widen dispersion, thereby increasing health inequality. In contrast, the high-risk strategy, whether targeted by the level of a single risk factor or of a composite risk factor score (56), may result in a truncation of the high-risk tail of the distribution, thereby reducing health inequality, and may simultaneously reduce social-group inequalities in health. It is important to note that reductions of both health inequality and social-group health differences requires an equitable allocation of resources, a condition often not met in the real world. The example of bariatric surgery shows that, in the United States, poor nonwhite women had the highest levels of morbid obesity (71), but white, high-income women with private insurance were the most likely to receive bariatric surgery (78, 79). Similar social-group health differences persisted even in a publicly funded universal healthcare system—in Canada, low-income women were <50% as likely as middle-income women to be approved for bariatric surgery (80, 81).

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The idea of reducing distributional measures of inequality is well established in fields such as economics, in which indexes such as the Gini coefficient, a measure of the distributional inequality in income, are frequently used (82). For example, when considering the distribution of income, policies to increase the income of individuals in absolute poverty is analogous to the high-risk strategy, and these policies are often instituted alongside the population strategy of increasing mean income. The ethical imperative might be even greater to focus on the poor, especially from an equity perspective.

CONCLUSIONS

In this Perspective, we have argued that Rose's concept of preventive medicine is anchored on the cohesiveness of populations, an assumption that may be violated by differential changes in the BMI distribution occurring globally within populations. The phenomenon of increasing dispersion may be a fundamental trait of population patterns of weight gain and also calls into question our ability to track population health, make statistical inference, and measure the impact of interventions when we focus disproportionately on the change in the mean. As dispersion rises, the value of the mean as a measure of a population decreases, but this simple reasoning has not entered into much of the global discourse around risk-factor changes (6–9), although it is promising to see that more recent articles have paid more attention to measures of variance when examining population trends (27). Although we reference the specific example of rising dispersion in BMI, further research is needed to see whether such patterns are also observed for other metrics such as waist circumference, blood pressure, blood glucose concentrations, or lipid concentrations. Why interindividual inequality is increasing and how much of this increase can be explained by known factors remain important areas of future scientific inquiry, with implications for developing evidence-based public-health policies that find a place for both the population strategy and the high-risk strategy for disease prevention and disease reduction.

An important question arises: when does increasing dispersion lead to a situation in which a multitiered intervention is needed rather than a single population strategy? There may be no simple answer to this question, and each new intervention may need to be evaluated for its appropriateness for all segments of the population. The situation described in India gives a clear example of opposing population needs and opposing interventions, in which the overweight and obese need to lose weight and the underweight need caloric and protein supplementation. In contrast, the situation in the United States is one of multiple interventions with a unified goal—weight loss through population-wide approaches such as increased exercise and reduced caloric intake—and additional focal interventions such as medication or surgery for the morbidly obese. In both situations, rising dispersion should be a flag for researchers and policy makers that a one-size-fits-all approach may not be appropriate or sufficient. Creating specific criteria or action thresholds to identify when rising dispersion requires multiple interventions is an important area of future study and may result in answers that depend on both the degree of dispersion and the risk and benefit profile of the specific interventions being considered.

Twenty-five years ago, Rose placed heavy emphasis on the study of the central tendency of a population (11, p. 1408):

> The study of individual susceptibility is important, but the fundamental questions are, "What determines the population's mean blood pressure, cholesterol, body weight, and alcohol intake? And how might that mean be changed?"

Twenty-five years later, in an era of rising inequality (83), we may need to move beyond this framework for population change and not only focus on measures of centrality but also consider questions of dispersion and the underlying factors that drive such increasing variation. Ultimately, it is individuals who develop diseases, even if what leads to an individual developing a disease will have its answers in factors that operate simultaneously at the individual and population levels.

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APPENDIX A

A historical perspective on populations as a statistical entity

Although the concept of "the population" is central to public health and epidemiology, its definition is surprisingly fuzzy. As Krieger (1) has discussed, it may be used *1*) in population sciences in a general sense to define the geography that a group inhabits (e.g., Canadians or Americans), *2*) in a technical sense to describe a genetic concept (a group in whom breeding can occur), *3*) to describe a subset of a larger group (e.g., the elderly or individuals with low income), or *4*) as a statistical entity (a group of individuals in whom meaningful statistical measures can be made through sampling). This final application, which is driven by statistical considerations, is what is most commonly used in population sciences, including in the ideas developed by Rose (2) and Keys (3).

The concept of populations as a coherent entity, amenable to summary statistical measures, was advanced in the first half of the 19th century when Quetelet (4) introduced his famous and controversial idea of the "average man" (1, 5). Quetelet was an advocate of what he called "social physics," the idea that human populations could be studied and summarized by using many of the statistical techniques developed in the natural sciences and mathematics (5). One of Quetelet's endeavors (4) included the development of an index of weight relative to height, which was termed the "Quetelet Index," until it was given its modern name of body mass index by Keys in 1972 (6). For much of his work, Quetelet drew analogies to his work in astronomy to better characterize human populations. When describing the ability of multiple observatories spread across Europe to triangulate the presence of celestial bodies by averaging their estimates and negating their individual errors in measurement, Quetelet felt that a similar feat could be achieved in human populations through a statistical summary of samples (1, 5, 7). Quetelet (8) was enamored with the rapidly expanding application of theory of the normal distribution (called the "law of possibility" by Quetelet) to measurements in the natural sciences and proposed (without proof) that the properties of the normal distribution could distinguish between what he called a "true mean" and an "arithmetic mean" (1, 5, 7, 8). Using the example of houses on a street, he stated that, if an individual was to repeatedly measure the height of a single house, there would be small errors in measurement that would be normally distributed around the "true mean," a value that would capture something innate and essential about the house. In contrast, if an individual was to measure the height of all of the houses on a street and took an average, this value would be only an "arithmetic mean," a purely statistical quantity with very little value in conveying anything about the collective nature of the houses, since each was designed differently (5). Quetelet acknowledged that differentiating between true and arithmetic means could be challenging but stated, without additional evidence that an individual would be able to identify true means because measured values would follow a normal distribution, whereas arithmetic means would not. With these claims, Quetelet then turned to human populations, examining a published tabulation of the chest circumference of 5738 Scottish soldiers and demonstrating a reasonable fit to the normal curve. The fact that these anthropometric measures were normally distributed proved for Quetelet (8) that all humans were imperfect replicates of an "average man." Thus, variations between individuals were labeled by Quetelet as simply errors in formation, with each man or

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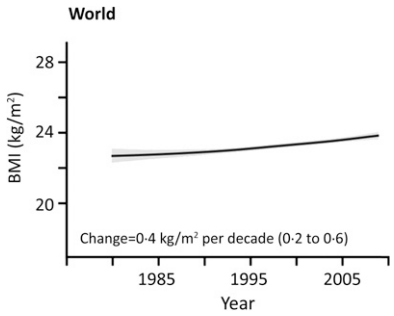

FIGURE A1 Global change in mean BMI from 1990 to 2008. Gray shading represents the 95% uncertainty interval. Reproduced from reference 11 with permission.

woman being an imperfect version of a true population ideal, thereby conflating true variation and imperfect measurement. From his humble observations around the chest circumference of soldiers, Quetelet (8) proceeded to develop a social theory around "the average man," a concept he used to measure and compare the physical, intellectual, and moral traits of entire countries, and in doing so, he laid the groundwork for more modern concepts such as Rose's "sick populations" (9). Although many of the ideas advanced by Quetelet may seem odd to a modern reader, we continue to be captivated by the idea of the intrinsic value of comparing, contrasting, and tracking national averages of a wide range of measures in population health (10–13), economics, and demography (14). For example, consider the major summary on global trends in BMI that was published in *The Lancet* that not only made claims about the ability to glean meaningful information from trending average BMI in regions as broad as Central Asia or West Africa but also proceeded to plot the mean change in BMI for the entire world over a 20-y period (**Figure A1**) (10). This sort of statistical reporting builds on a tradition extending from Quetelet onward, but one is left wondering at the adequacy of the mean in understanding anything about the health and well-being of >7 billion people. As Francis Galton observed >100 y ago in his treatise *Natural Inheritance*, much is lost through our narrow-minded focus on population averages (15, p. 62):

> It is difficult to understand why statisticians commonly limit their inquiries to Averages, and do not revel in more comprehensive views. Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if it's mountains could be thrown into its lakes, two nuisances would be got rid of at once.

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