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## PREVENTION OF STROKE: A STRATEGIC GLOBAL IMPERATIVE

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### Abstract

The increasing stroke burden in the world strongly suggests that currently implemented primary stroke prevention strategies are not sufficiently effective, and new effective primary prevention strategies with larger effect size are needed. In this article, we reviewed the latest stroke epidemiology literature with the emphasis on the recent Global Burden of Disease 2013 Study stroke burden estimates from 1990 to 2013, highlight the problems with current primary stroke and cardiovascular disease (CVD) prevention strategies, and outline new developments in primary stroke and CVD prevention. We also suggested key priorities for the future, including comprehensive prevention strategies that target people with all levels of CVD risk, implementation of an integrated approach to promote health behaviors and reduce health disparities, capitalizing on information technology to advance prevention approaches and techniques, and incorporation of culturally appropriate education about healthy lifestyle into standard education curricula early in life. Given the already immense and fast increasing burden of stroke and other major noncommunicable diseases (NCDs) which threatens worldwide sustainability, governments could develop and implement an emergency action plan addressing the primary prevention of NCDs.

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#### Conflict of interest

Valery L. Feigin declares that Stroke Riskometer™ app is copyrighted by the Auckland University of Technology and funds resulting from the sale of the professional version of the Stroke Riskometer App will be used for further research and education for stroke prevention. All other authors declare that they have no conflict of interest.

#### Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; National Institutes of Health; Centers for Disease Control and Prevention, or the U.S. Department of Health and Human Services.

## Keywords

stroke; primary and secondary prevention

Stroke remains a major global health problem<sup>1</sup> and its significance is likely to increase in the future due to ongoing demographic changes, including ageing of the population and health transitions observed in developing countries.<sup>2,3</sup> The Global Burden of Disease (GBD) Study provides the most comprehensive assessments of the state of health in the world since 1990.<sup>4</sup> The most recent assessment of the global, regional and country-specific burden of stroke is the 2013 study (GBD 2013), which provides results for 1990, 2005 and 2013. Data from the GBD 2013 Study showed that while age-standardized rates of stroke mortality have decreased worldwide in the past two decades, there was a significant increase in the absolute number of people affected by stroke worldwide from 1990 to 2013.<sup>3</sup> There is currently almost no country in the world where the stroke burden in terms of absolute number of incident and fatal strokes, stroke survivors and disability-adjusted life years (DALYs) has reduced. The increasing stroke burden in the world strongly suggests that currently used high-risk and population-wide primary stroke prevention strategies are not sufficiently effective, and more effective primary prevention strategies with larger effect size are needed.

In this article, we provide an overview of the most recent literature on stroke epidemiology with the emphasis on main results of the GBD 2013 Study concerning ischaemic stroke (IS) and haemorrhagic stroke (HS) burden in the world in children and adults in 1990 and 2013 by sex, highlight problems with current primary stroke and cardiovascular disease (CVD) prevention strategies, outline several new developments in primary stroke and CVD prevention and suggest key priorities for actions.

## THE GLOBAL BURDEN OF STROKE

The main results of the GBD 2013 stroke burden estimates were published in a special free-access issue of *Neuroepidemiology*<sup>3,5–11</sup> in October 2015. In 2013, there were almost 25.7 million stroke survivors (71% with IS), 6.5 million deaths from stroke (51% died from IS), 113 million DALYs due to stroke (58% due to IS), and 10.3 million new strokes (67% IS).<sup>3</sup> There were large geographical variations in IS and HS age-adjusted incidence, prevalence and mortality rates (Figures 1 and 2). The highest prevalence rate of IS (1,015–1,184/100,000) was observed in developed countries (particularly USA), the lowest (up to 339/100,000) in developing countries. The highest IS mortality rates (124–174/100,000 person-years) were observed in Russia and Kazakhstan, and the lowest (at or below 25/100,000) – in Western Europe, North and Central America, Turkmenistan and Papua New Guinea. Prevalence rates of HS were highest (232–270/100,000) in the USA, and lowest (up to 78/100,000) in Latin America, Africa, Middle East, France, Eastern Europe, Northern part of Asia and Russia. HS mortality rates were highest (159–222/100,000 person-years) in Mongolia and Madagascar, and lowest (up to 32/100,000) in North America, most parts of Western Europe, Russia, Iran, Saudi Arabia, Morocco, Japan, Australia and New Zealand (Figure 2). These geographical variations in stroke burden emphasize the need for regional-specific approach for stroke care planning and prevention.

Globally, over the last few decades stroke burden in terms of absolute number of people affected by and died from stroke has increased dramatically<sup>1,3</sup> largely due to ageing of the population and population growth in most regions,<sup>2</sup> and there were no countries in the world where this burden was declining.<sup>12</sup> Over the 1990–2013 period, there was a significant increase in the absolute number of disability-adjusted life-years (DALYs) due to IS, and of deaths from IS and HS, survivors and incident events for both IS and HS (Box 1) in both men and women.<sup>1,3,9,10,13</sup> The bulk of the burden of stroke continued to reside in developing countries, where it comprised 75.2% of the global deaths from stroke and 81.0% of the global stroke-related DALYs (Figure 3). Globally, the proportional contribution of stroke-related DALYs and deaths due to stroke compared to all diseases increased by about 20–25% from 1990 (3.5% [95% uncertainty intervals (UI) 3.1 to 4.0] and 9.66% [95% UI 8.5 to 10.7], respectively) to 2013 (4.6% [95% UI 4.0 to 5.3] and 11.8% [95% UI 10.5 to 13.3], respectively). However, there was a diverging trend in developed and developing countries. For example, there was a significant increase in DALYs and deaths in developing countries, and no measurable change in the proportional contribution of DALYs and deaths from stroke in developed countries. While the proportional contribution of IS-related DALYs and deaths to DALYs and deaths from all causes was greatest in developed countries, for HS these proportions were greatest in developing countries (Figure 4). While the increase in the incidence of HS in developing countries may be related to the high rate of undetected and/or poorly controlled arterial hypertension,<sup>14–17</sup> stroke incidence increase<sup>18</sup> or even better detection of stroke in those countries, the increase in the prevalence of IS and HS in developed countries could be related to the improvements in acute stroke care, or more effective secondary prevention and greater identification of minor stroke cases (including wider use of advanced neuroimaging),<sup>19</sup> which is highly dependent on universal access to primary care.<sup>20,21</sup>

Of additional concern is a significant increase in the number of younger adults (aged <65 years) affected by stroke.<sup>1,22,23</sup> In 2013 there were 97,800 [95% UI 90,600 to 106,000] prevalent cases of childhood IS and 67,621 [95% UI 62,900 to 72,200] prevalent cases of childhood HS, reflecting an increase of approximately 35% in the absolute numbers of prevalent childhood strokes since 1990.<sup>8</sup> Between 1990 and 2013 there were significant increases in the global prevalence rates of childhood IS, as well as significant decreases in the global death rate and DALYs rate of all strokes in 0 to 19 year olds. While prevalence rates for childhood IS and HS decreased significantly in developed countries, in developing countries, a decline was seen only in HS, with no change in IS prevalence rates. In 2013, the prevalence rate of both IS and HS in children was significantly higher in developed countries than developing countries. However, both death and DALY rates for all strokes in children were significantly lower in developed countries than in developing countries in 2013. Also, between 1990 and 2013 there were significant increases in prevalent cases, total deaths, and DALYs due to HS and IS in younger adults (20–64 years).<sup>9</sup> If these trends continue, the burden of stroke will increase even faster<sup>24</sup> and the UN Global Targets<sup>25</sup> to reduce premature mortality from non-communicable diseases (NCDs), including stroke, by 25% by 2025 will not be met. Moreover, for stroke in particular, mortality reduction should not be the primary health goal<sup>12</sup> because about three quarter of stroke survivors remain disabled and reduced mortality will inevitably lead to a greater number of people disabled from

stroke. Focus on acute phase treatment and rehabilitation alone will not significantly reduce the burden of stroke.<sup>26</sup> There is an urgent need to address these disparities in stroke burden in children and young adults (taking into account some specific causes for childhood stroke)<sup>27</sup> with both global and country level initiatives targeting prevention early in life as well as improved access to acute and chronic stroke care.<sup>8</sup>

The GBD 2013 Study also demonstrated important sex differences in IS and HS burden in the world.<sup>10</sup> In 2013, men had a higher incidence of IS than women while significant sex differences in the incidence of HS were not observed (Figure 5). The total DALYs were similar for men and women for both stroke subtypes in 2013. Both IS and HS DALYs showed an increasing trend for both men and women since 1990 which was statistically significant only for IS among men. These findings show a clear need for additional research into factors that potentially contribute to the causes of sex differences in risk and outcomes. In addition, there is adequate evidence of differences in stroke incidence and burden between the sexes to support the need for well-designed stroke intervention trials, which are equally powered for men and women to examine effectiveness of primary care, risk factor management strategies, and hospital services.<sup>10</sup>

Stroke is currently the third largest contributor to DALYs after ischemic heart disease and lower respiratory infection globally in developing countries, and it is third largest contributor to DALYs in developed countries (after ischemic heart disease and low back and neck pain).<sup>28</sup> This emphasizes the importance of stroke as a leading global health problem that requires urgent attention from governments, health care policy makers, international agencies, clinicians, public health specialists and individual citizens. Therefore, preventing new strokes is the core solution to the problem of growing stroke burden. Although mainstream preventative strategies should be similar in developed and developing countries (e.g. a combination of population-wide and high-risk prevention strategies), differences in the epidemiology of stroke (including differences in the prevalence and relative significance of risk factors) as well as resources available for stroke prevention should be taken into account when setting up realistic goals, priorities and means. For example, given the differences between developing and developed countries in terms of stroke burden (particularly the greater proportion of stroke in young adults and much greater burden from HS in developing countries compared to that in developed countries), a strong emphasis on early detection and management of elevated blood pressure should be a priority in developing countries. In developed countries, where the stroke burden associated with IS is noticeably greater than that in developing countries, it seems reasonable to focus more heavily on reducing behavioural risks (particularly diet, physical activity, overweight) and managing medical conditions leading to atherosclerosis. While the prevalence of behavioural and other modifiable risk factors of cardiovascular disease (CVD)<sup>29</sup> including stroke has reached epidemic proportions worldwide,<sup>30,31</sup> there is evidence that modifying health behaviours is feasible, improves health outcomes, reduces healthcare costs,<sup>32</sup> can arguably reduce an individual's risk of stroke by about 80%<sup>33,34</sup> and reduce stroke incidence by about 50%.<sup>35</sup> There is also evidence for more aggressive blood pressure control for stroke prevention even in people with borderline hypertension and without diabetes with a systolic blood-pressure target of less than 130 mm Hg.<sup>36,37</sup> Another very important and prevalent risk factor for stroke the management of which has recently dramatically changed is atrial fibrillation (AF).

<sup>38</sup> As the incidence and prevalence of AF (including paroxysmal AF) is increasing,<sup>39–41</sup> there is an urgent need to better detection and wider implementation of modern treatment for AF. However, the ever-increasing burden of stroke across the globe, large sex and racial/ethnic disparities and a trend towards more strokes in younger people in both developed and developing countries all indicate deficiencies in current stroke prevention strategies. More efficient stroke prevention strategies are urgently needed to halt and eventually reverse the stroke pandemic.<sup>3</sup> However, before discussing new, potentially more effective stroke prevention strategies it is important to untangle causes of insufficient effectiveness of the currently used strategies.

## APPROACHES TO STROKE PREVENTION

Population-wide strategies together with strategies that target high-risk individuals have been proposed as the most effective for stroke prevention.<sup>42</sup>

### Population-wide strategies

Population-wide strategies are essential because even small changes in the distribution of risk factors would lead to major reductions in stroke/CVD incidence in the population (Figure 6).<sup>43,44</sup> The population-wide prevention strategy was suggested by Sir Geoffrey Rose in 1985 as the most effective strategy for primary CVD prevention.<sup>44</sup> As this strategy targets several behavioural and lifestyle risk factors (including tobacco use, unhealthy diet, physical inactivity, overweight and the harmful use of alcohol) that are common for a range of major NCDs, such as heart disease, diabetes, cancer, dementia and pulmonary heart disease, this strategy will be positively impacting not only stroke risk but on all these major NCDs. Over the last 15 years, it has been included in all major CVD prevention guidelines,<sup>34,45</sup> often in combination with high-risk approach and with several anecdotal reports of its effectiveness in selected populations.<sup>46–48</sup> Nevertheless, there is still no country in the world where this strategy has been implemented in full at the national level. The major reasons for the lack of implementation of this strategy on a national level include costs (e.g. increasing the availability of facilities for physical activity, healthy food outlets) and the need for policy and legislative changes that are often not supported by major industries (e.g. salt reduction in processed food, reduction of exposure to smoking, alcohol, fast food).<sup>24</sup>

An additional important benefit of population-wide prevention approaches that target the entire population rather than just those at high risk is that it may be easier and more effective to promote the maintenance of health than to reverse existing damage, therefore, sensitive timepoints at which health changes may be most impactful are likely earlier in life before subclinical risk factors have emerged.

### High-risk strategies

Intensive clinical care for high-risk individuals remains the dominant paradigm in the world for prevention of stroke.<sup>49</sup> While management strategies for primary stroke prevention in high CVD risk individuals are well established,<sup>34</sup> they are under-utilised<sup>34,50–53</sup> and existing methods of primary stroke prevention are not sufficiently effective.<sup>54–56</sup> The healthcare system has been largely unsuccessful in providing relevant meaningful information to assist

people in adhering to recommended lifestyle changes and medications.<sup>34,54,55,57–59</sup> Uptake of primary prevention recommendations is particularly low in people with moderately increased risk of stroke who would benefit from lifestyle modifications.<sup>54,59,60</sup> Inadequate CVD risk factor management<sup>54,55</sup> and lack of effective communication between health professionals and stroke patients/family<sup>54,61–63</sup> are implicated in underutilisation of primary stroke prevention strategies in people with moderately increased risk of stroke.<sup>61</sup>

The high-risk prevention strategy implies calculation of absolute risk of CVD over the next 5 or 10 years with the aim of identification of people at high risk of development of acute CVD (heart attack, stroke, acute peripheral artery disease), which usually defined as having a risk of 15% over the next 5 years or 30% over the next 10 year or having an established CVD (e.g. stroke, ischemic heart disease, transient ischemic attack [TIA], peripheral artery disease).<sup>64,65</sup> Although assessment of people for absolute stroke/CVD risk is important for matching the intensity of preventing efforts with the individual's absolute risk<sup>66</sup> and monitoring success or failure in primary stroke/CVD prevention, there several major issues with the high-risk approach for stroke/CVD prevention. Primary stroke/CVD prevention strategy that aims primarily at high-risk individuals fails to engage into active prevention the majority of the population where most strokes and other acute CVD events occur,<sup>67,68</sup> it also lacks personal motivation to control risk factors by people who are at low or moderate risk of CVD events. Other limitations of this strategy include costs associated with laboratory tests and doctors visit to determine the risk, and lack of population-specific algorithms for stroke and CVD prevention.<sup>24</sup> There is evidence that even effective population-wide use of high-risk prevention strategies with aggressive pharmacological treatment in individuals with a 10-year Framingham event risk of 30% (6% of population) would have reduced major CVD by at most 11%,<sup>49</sup> and if high-risk strategies are to have a major impact on CVD in the population, they need to be more widely used than previously envisaged.<sup>49</sup> In addition, the use of high-risk prevention strategies is limited by access to medical professionals,<sup>69</sup> and even when care is available, the adherence of patients to recommended medications and lifestyle modifications are often poor<sup>70</sup> due to multiple reasons,<sup>71</sup> including wrong patients' beliefs<sup>72</sup> (limited health literacy) and comorbidities.<sup>73</sup>

Although it is generally agreed that screening for CVD risk can be used as a guide for making clinical decisions on the intensity and effectiveness of preventative interventions,<sup>42,74</sup> just screening of the population for CVD risk in order to provide intensive medical care to high risk individuals continues to be thought of as an important health target by many governments.<sup>75</sup> This is particularly disappointing because there is compelling evidence from 15 large randomized controlled trials (totalling about 200,000 patients), including Cochrane systematic review and meta-analysis,<sup>76,77</sup> that screening for high CVD risk, even in combination with some counselling,<sup>77</sup> is not effective for reducing CVD incidence and mortality. The lack of effectiveness of just screening of the population for high CVD risk individuals and ethical concerns about promotion of screening without linkage to diagnosis and management has led some governments to explore additional ways to improve CVD prevention. For example, the use of CVD predicting algorithms in combination with incentivising clinicians for effective CVD prevention is being trialled in the USA,<sup>78–80</sup> and the most recent evidence suggests that incentivising both clinicians and patients works.<sup>81</sup> While shared financial incentives shown to be effective in that trial for reducing LDL-C level

(US\$512 per patient for physicians and US\$355 for each patient enrolled in the trial) may not be feasible in less affluent societies, the findings of the importance of motivating *both* physicians and their patients for effective CVD prevention should not be underestimated and some other, more affordable incentives can and should be trialled in other populations.

### **A combination of population-wide and high-risk strategies**

Primary prevention of stroke and other major NCDs is regarded by the UN as the most cost-effective strategy to reduce burden from these diseases.<sup>82</sup> For example, reducing salt intake by 15% and implementing four key WHO elements of reduction in tobacco use (taxation, enforcement of smoke-free workplaces, packaging/labelling requirements, awareness campaigns) could avert 13.8 deaths over 10 years at a cost of less than US\$0.4 per person per year in low-income and lower middle-income countries, and only US\$0.50–1.00 per person per year in upper middle-income countries.<sup>83</sup>

It is essential for high-risk stroke prevention strategies aimed at specific high-risk populations (e.g. people with stroke or TIA, atrial fibrillation, sickle cell disease, etc.) to be accompanied by population-wide prevention strategies aimed at behavioural/lifestyle and environmental risks in which responsibilities are shared between the health sector, non-government organizations and government bodies. While certain governmental bodies have the power to inform or influence lifestyle, socio-economic and environmental factors (including tobacco control, healthy nutrition, bike lanes, availability of fruits and vegetables at corner stores, air pollution) as well as to provide adequate health services to ensure universal implementation of preventative strategies, the health system has the responsibility to identify risk factors and their proper management on an individual level.<sup>84,85</sup> While these integrative, cross-sectoral approaches combined with behavioural modification (including stroke preparedness and lifestyle modifications) and other strategies have been recently identified as the key strategies for stroke and CVD prevention,<sup>26,59,86</sup> the difficult question is – what could make stroke prevention work? How best to combine population-wide and high-risk prevention strategies? Here are our four major suggested strategies to improve primary stroke prevention (Box 2).

## **IMPROVING PRIMARY STROKE PREVENTION**

### **Shifting the emphasis**

*The emphasis in primary stroke prevention should be shifted from high stroke/CVD absolute risk approach to a more comprehensive approach that includes primary stroke prevention strategies in people with all levels of risk of CVD events.* In addition to more aggressive controlling elevated blood pressure and other metabolic/physiological risk factors (including AF), primary stroke prevention needs to focus on behavioural and lifestyle risk factors (including tobacco use, unhealthy diet, physical inactivity and the harmful use of alcohol) allowing an integrative approach to primary prevention of other major NCDs, such as heart disease, diabetes, cancer, dementia and pulmonary heart disease. This cluster of diseases and risk factors are prioritized by the World Health Organization (WHO) in its Global Action Plan on NCDs<sup>87</sup> and included in the 2011 UN NCD Declaration, and the UN Post-2015 Sustainable Development Goals.<sup>12</sup> In stroke/CVD occurrence predicting algorithms used by

health professionals for stroke/CVD prevention educational purposes, categorising people into low, moderate and high absolute risk for the purpose of communicating the risk to the patients should be abandoned as it discourages people with low and moderate risk of CVD to be motivated to reduce their risk and engaged into primary prevention programmes.<sup>24</sup> To illustrate increased risk for people with low absolute CVD risk, it was recommended to use a relative risk, relative risk charts, lifetime risk,<sup>24,88,89</sup> and various risk visualization techniques.<sup>89–91</sup> People with 10-year absolute CVD risk less than 30% should be empowered by their health professional (e.g. by showing them not only their absolute but also relative risk and the effect that each risk factor exposure reduction has on their risk) to control their modifiable risk factors, improve CVD health and reduce their risk of stroke/CVD to as low as possible level. In addition to healthy lifestyle modification<sup>92</sup> and better adherence to the recommended medications,<sup>93,94</sup> multidrug regimens of proven effective and cheap drugs (e.g. polypill)<sup>95</sup> could lead to cost-effective prevention of stroke in all developing regions, potentially halving the risk of death from CVD and increasing life expectancy.<sup>96</sup>

### An integrated approach

*Implementing an integrated approach would incorporate community-clinical linkages that coordinate clinical strategies for high-risk individuals with community-based strategies to promote healthy behaviours and reduce health disparities.*<sup>97,98</sup> Coordinated interventions allow for community-wide prevention and management approaches that link efforts improving health across the care continuum and bridging across settings and strategies. Community-clinical linkages help ensure that people with or at high risk of chronic diseases have access to community resources and support to prevent, delay or manage chronic conditions once they occur.<sup>99</sup> These supports include interventions such as clinician referral, community delivery and payment coverage for effective programs that increase the likelihood that people with heart disease, diabetes or pre-diabetes will be able to “follow the doctor’s orders” and take charge of their health.<sup>99</sup> Examples include clinical strategies to promote individual smoking cessation along with smoke-free laws that reduce secondary exposure, or the use of community health workers and community pharmacists that can extend the work of the clinical provider into the community and broader population.<sup>100</sup> Given the limited resources available for stroke and CVD prevention even in developed countries, it would be logical to place emphasis on effective population-wide interventions to control or reduce exposure to leading risk factors in the region. For example, population-wide efforts to reduce salt intake and smoking through multiple economic (e.g. taxation) and educational policies and programs have been suggested as cost-effective primary stroke and CVD strategies in developing countries.<sup>101–105</sup> With the UN 2011 Declaration of NCDs,<sup>12</sup> all UN-member governments have the mandate, power and responsibility to undertake actions to reduce the burden from NCDs, including stroke. The practical question is where to take resources to enable these actions? We believe that revenue from smoking and salt taxations, as well as taxations from sugar and alcohol, reduced consumption of which on a population level also shown to be beneficial for CVD and overall health,<sup>106,107</sup> can and should be used to fund primary prevention strategies and primary prevention research of stroke and other major NCDs. Such uses of the tax revenue would also be important to ensure public acceptability of these taxes.<sup>108</sup> There is compelling evidence that smoking,



109–111 salt,<sup>83,108</sup> sugar<sup>112–114</sup> and alcohol<sup>115–119</sup> taxation may be valuable strategies to improve health, especially when combined with other preventative interventions in the population, while generating a considerable revenue for governments.<sup>113,120–122</sup> Given the already immense and fast increasing burden of stroke and other major NCDs across all countries in the world that threatens sustainability of the whole society, not acting now on primary prevention of these diseases is not acceptable. Governments can develop and implement an emergency action plan addressing the primary prevention of NCDs. It is also important to work on the implementation of what has proved working for primary stroke and NCDs prevention over the last decades in many developed countries in a broader way.

### Using information technology

The impact of stroke and other non-communicable disorders (NCD) that share the same risk factors with stroke, such as ischemic heart disease (IHD), dementia (cognitive decline) and type II diabetes mellitus, is huge and increasing.<sup>123–125</sup> Collectively, these NCD account for 14.7 million of deaths (28% of deaths from all causes)<sup>125</sup> and 290.2 million disability-adjusted life-years lost worldwide.<sup>124</sup> The burden of NCD is likely to burgeon given the aging of the world's population and the epidemiological transition currently observed in low- to middle-income countries.<sup>126</sup> In addition, there is low awareness in the population about these NCD and their risk factors, particularly in developing countries. These factors, coupled with underutilization of strategies for primary prevention of NCD on an *individual level* and the lack of accurate data on the frequency and significance of risk factors in different countries and populations have been implicated in the ever-increasing worldwide burden of the NCD.

Recent advances in mobile (smartphone) technologies and their worldwide use (about 1.7 billion users) offer unique opportunities to utilise these technologies for improving health (including health and stroke awareness) and research capabilities. Empowering people for self-management of their risk factors through mobile health apps is another potential application of these technologies, which may be particularly appealing for less affluent populations and population with limited access to health services (e.g. rural populations). A number of stroke and other NCD Apps are currently available in App Store and Google Play and promising results are emerging from clinical trials of several smartphone-based technologies and Apps for managing particular medical conditions and risk factors (e.g., smoking cessation, depression, weight and asthma management).<sup>127–131</sup>

*Primary stroke prevention should capitalize on information technology* to advance prevention approaches and techniques. Electronic health information can be useful to support patients, providers and population health, such as through improved public health surveillance activities.<sup>132</sup> Importantly, accumulating evidence demonstrates the feasibility and effectiveness of use of mobile technologies for improving healthy lifestyle<sup>133–139</sup> and some medical conditions predisposing to stroke.<sup>140–145</sup> Supported by WHO,<sup>146</sup> these technologies are evolving fast<sup>147</sup> and have shown unprecedented uptake amongst lay consumers and professionals.<sup>148</sup> Use of widely accessible, affordable and validated technological advances,<sup>147</sup> such as the Stroke Riskometer™ app,<sup>24,149</sup> to recognize a person's own risk and risk factors, to educate about warning signs of stroke that can

communicate risk and the importance of addressing risk factors that speak to a various levels of health literacy and in multiple languages, to motivate the person to control their risk factors, to provide targeted advice on how to lower the risk, and to measure effectiveness of primary prevention of NCDs, is another important approach for stroke prevention that should be incorporated into the health system and used by both health professionals and lay people. Not downplaying their significance for developed countries, such mobile technologies are particularly useful for developing countries where availability/affordability of and access to health professionals are limited. Such self-care programs are also seen by the WHO<sup>150</sup> as a vital form of prevention in those at high risk and in improving outcomes in people with NCDs.

### **Culturally appropriate health education**

As there are significant disparities in the risk<sup>151–155</sup> and burden of stroke among various race/ethnic groups<sup>151–155</sup> and many life style habits are set early in life, *culturally appropriate education about healthy lifestyle should be incorporated into standard education curricula and started early in life with reinforcement across the lifespan*. There is evidence suggesting effectiveness of school-based stroke education of middle school children,<sup>156</sup> and it may be possible that trained children and community leaders can be effective healthy lifestyle educators for other children. In addition to health being a physical manifestation, stroke knowledge is also a socio-cultural construct that can limit the utility of universal primary prevention strategies for at-risk groups.<sup>8–10</sup> Therefore, it is essential to understand the views, values, norms and beliefs of peoples of varies race/ethnicity who are at risk of stroke, what is more likely to work for them in order to learn and understand stroke and its associated risk factors, and how they will use this information to modify what they do in their daily life. Evidence suggests that even if an intervention is effective, adherence to its recommendations remains poor unless it is meaningful, acceptable and takes into account the factors that make up the patients' health care environment.<sup>157</sup> In addition, it has been shown that people's beliefs are important predictors of the extent to which they will engage in behaviours to reduce risk of secondary stroke.<sup>71</sup> Therefore it is crucial that stroke prevention strategies take these factors into account to have optimal impact. This information may also be used to inform culturally appropriate preventative strategies of other major NCD that share common risk factors with stroke, such as CVD, dementia and diabetes.

Linguistic and cultural (subcultural) differences between people of different race/ethnicity in relation to social, family values and sex and gender roles should be taken into consideration when developing culturally competent health education programs.<sup>158</sup> For example, healthy diet recommendations that are successful for stroke and CVD prevention in people of Caucasian ethnicity may not be successful for Pacific or Asian people because their food habits and traditions are very different. There are also racial/ethnic differences in the relative significance of various determinants of stroke occurrence<sup>152</sup> that should also be taken into account when developing culturally specific health education programs. Generic guidelines for making a health education programme more culturally appropriate have been suggested.<sup>158</sup> Development of consensus statements and national stroke prevention guidelines by recognised experts from the region to address local (cultural) issues on the basis of the best

available evidence along with the effective strategies to improve stroke awareness (including campaigns to remove stigma associated with stroke) should also be encouraged.<sup>101</sup> Mother's health and lifestyle, normal birth weight, adequate nutrition from the first days of life and thereafter are all-important determinants of health, including risk of stroke and other major NCDs, later in the life. Healthy lifestyle habits, adequate physical activity and maintaining a healthy weight should be formed at a young age,<sup>159</sup> reinforced throughout the lifespan (for healthy diet habits, probably during the first year of life),<sup>160</sup> and can be successfully incorporated in preschool, school, day-care and other interventions in early life settings.<sup>161</sup>

Recent studies in other countries have shown that knowledge of stroke risk factors and warning signs is deficient in older adults (65+),<sup>162,163</sup> minority ethnic groups,<sup>163–166</sup> people with low levels of education<sup>163</sup> and rural dwellers.<sup>167</sup> Consistent, culturally sensitive and motivational stroke education campaigns throughout the year (not only at national or World Stroke Awareness day) should be given a priority. As such campaigns are unlikely to be funded by the industry, but there are opportunities for the public sector to promote stroke awareness educational campaigns (along side of other educational campaigns). There is compelling evidence that increasing population/country-specific knowledge about stroke warning signs and risk factors can reduce stroke burden in the population.<sup>168–173</sup>

## FUTURE RESEARCH DIRECTIONS IN PRIMARY STROKE PREVENTION

More good quality research is urgently needed on risk factors and prevention of stroke (major stroke pathological types and ethological subtypes) in various countries and populations, including research to untangle the causes of the increasing burden of stroke in developing countries and causes of changes in trends and projections of stroke burden in men and women of different age and race/ethnicity, especially research to investigate interventions for the ageing population, and strategies for implementation that can remain cost-effective for larger and larger population. Although mortality from stroke has declined substantially in developed countries, the use of proven strategies for stroke and CVD prevention, even in wealthy countries, is far from optimum. Stroke and CVD rates can be further reduced in future not only with more widespread implementation of proven strategies, but a greatly improved understanding of regional and ethnic variations of the causes of stroke because understanding of the risk factors for stroke and stroke types (including their population-attributable risk) in different race/ethnic populations is crucial to determining priorities and strategies for targeted stroke prevention in these populations.<sup>29</sup> While population-wide strategies for primary prevention of NCDs have been proven feasible and effective,<sup>46–48</sup> more research is warranted on the best, culturally appropriate and cost-effective ways of implementing these strategies on a population level, including their combination with high-risk strategies, self-management and knowledge transition research. More definitive research, including digital health research and randomized controlled trials in various populations sufficiently powered by sex, race/ethnicity and various age groups, are required for behavioural and educational interventions to specifically prevent stroke. However, primary prevention research is expensive, commonly not supported by industry, often regarded as 'non-sexy' research by research funding agencies, and there is obvious lack of research funding even in affluent countries, especially for stroke research.<sup>174</sup> Therefore, there is an obvious question where to get funding for primary prevention research

and how it can be best managed? Given the very applied nature of such research, research initiatives could improve the evidence base for primary prevention strategies.

The World Health Federation's recommendation for cardiovascular disease prevention (including stroke) includes conducting "large population studies in different regions of the world as the types and patterns of diet, activity, alcohol consumption, and tobacco use vary by region; regional studies are essential to document their effect in each region".<sup>86</sup> This recommendation recognizes the importance of region/country specific data on stroke risk and causative factors. The NIH NINDS Stroke Progress Review Group 2012 recommended three top priorities for future stroke epidemiology; (1) improving the understanding of race and ethnicity in stroke disparities; (2) evaluation of the usefulness of health information technology as a tool for epidemiology research; and (3) translating knowledge from epidemiological studies into improved health. Moreover, given race and ethnicity are confounded by socioeconomic and cultural factors, cultural contexts are essential to capture differences in contributing factors to stroke risk, such as language barriers, and access to healthcare. A study comparing CVD events in low vs high income countries has shown that while the prevalence of risk factors may be low in low-income countries, better control and more frequent use of proven therapies has mitigated the burden of stroke in high income countries, implying that contributing influences other than risk factors, such as access to and affordability of services, medications and treatments, as well as educational levels also affect outcomes.<sup>175</sup>

Given limited resources for carrying out national and international epidemiological studies (especially in developing countries), exploring new strategies for conducting such studies using mobile technologies seems appropriate. Recent advances in smartphone technologies including high processing power, storage, constant internet connection, personalised notification methods, growing worldwide uptake, and proximity to the users, offer unique opportunities to utilise these technologies for improving health and enhancing research capabilities.<sup>24</sup> There are numerous stroke and other NCDs smartphone applications (apps) currently available in the Apple Store and Google Play. There are also several smartphone-based technologies and apps that were, or are, being used in clinical trials for managing particular medical conditions and risk factors (e.g., smoking cessation, depression, weight and asthma management),<sup>127-131</sup> with promising results. In recognition of the importance of digital technologies for health, the UN Economic and Social Council, the International Telecommunication Union (ITU) and the WHO have recently (2013) launched a new mHealth initiative for improving NCD prevention, treatment and policy enforcement.<sup>176</sup> A good example of such affordable, ongoing large-scale smartphone-based worldwide cross-section and prospective cohort study on stroke risk factors is a study called RIBURST (Reducing the International Burden of Stroke Using Mobile Technology Study).<sup>24</sup>

New discoveries in stroke risk factors can be expected when genetic, environmental, behavioural and medical/physiological determinants are considered in combination and their interplay, with the involvement of a multidisciplinary team of experts (including clinicians, epidemiologists, geneticists, biostatisticians, mathematicians, computer scientists). The 2nd of the top three priorities in The Stroke Progress Review Group 2012 report for future directions of stroke research includes "Focus future biomarker development on markers of

small vessel disease severity and location, integrating these into multimodal studies of existing imaging markers, biochemical and genetic risks, and epidemiologic factors (including variations related to racial/ethnic/demographic group), aimed ultimately at unraveling the precise connections between vascular pathology, neurodegenerative pathology, and neurological impairment".<sup>177</sup>

Further research is also required in advancing precision medicine approach for stroke prevention recently introduced in the US<sup>178</sup> (including personalized prediction models of stroke), designing and clinical testing of pragmatic, potentially widely applicable (affordable) primary stroke prevention interventions in people of different sex, age and race/ethnicity, including proper assessment of promising indigenous medicines (including supplements) claiming CVD preventative properties. There is also a need for qualitative studies to explore how we can effectively design primary stroke prevention strategies to address potential barriers to implementation of medication and lifestyle changes known to reduce risk of primary stroke for those at risk.

## CONCLUSIONS

As stroke is being identified as one of the prioritized NCD in the WHO and UN actions on NCDs and new recent developments in stroke prevention, primary stroke prevention has entered a new era in which UN, WHO, government bodies, medical systems and non-government organizations must work together. Our hope is that the promotion and endorsement of new, proven effective approaches for the prevention of stroke and CVD, in combination with previously endorsed, high-risk and population-wide prevention strategies, will change current practice worldwide and, as a consequence, save millions of lives. When cost-effective health-care individual interventions are complemented with population-wide prevention strategies focusing on population-wide cardiovascular health rather than disease risk, a significant impact can be made on the global NCD epidemic.<sup>150,178</sup>

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**Box 1.**

Total number of DALYs, deaths, incident and prevalent cases of ischaemic and haemorrhagic stroke in the world in 1990 and 2013 (modified from Feigin et al.<sup>3</sup>)

		1990 (in millions)	2013 (in millions)	% Increase
<b>Ischaemic stroke</b>	<b>DALYs</b>	34.2 (29.6 – 38.3)	47.4 (40.5 – 52.2)	38.6%
	<b>Deaths</b>	2.2 (1.9 – 2.4)	3.3 (2.8 – 3.6)	50%
	<b>Incidence</b>	4.3 (4.1 – 4.5)	6.9 (6.5 – 7.4)	60.5%
	<b>Prevalence</b>	10.0 (9.6 – 10.5)	18.3 (17.8 – 18.9)	83%
<b>Haemorrhagic stroke</b>	<b>DALYs</b>	56.0 (49.9 – 62.2)	65.5 (59.5 – 74.7)	17%
	<b>Deaths</b>	2.4 (2.1 – 2.7)	3.2 (2.9 – 3.7)	33.3%
	<b>Incidence</b>	1.9 (1.8 – 2.0)	3.4 (3.2 – 3.5)	78.9%
	<b>Prevalence</b>		7.4 (7.1 – 7.6)	89.7%

**Box 2.****Key priorities for effective primary stroke prevention****Lifestyle factors**

- Shift the emphasis in primary stroke prevention to a more comprehensive approach that includes primary stroke prevention strategies in people with all levels of risk of CVD events
- Focus on behavioural and lifestyle risk factors (including tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol)

**Partnering Across Sectors**

- Shared involvement and responsibilities of health sector, non-government organizations and government bodies for the development and implementation of population-wide and high-risk prevention strategies to control stroke/NCDs
- Implement an integrated approach that incorporates community-clinical linkages to coordinate clinical strategies for high-risk individuals with community-based strategies that promote healthy behaviours and reduce health disparities
- Incentivise health professionals and patients for effective stroke/NCD prevention

**Electronic Health Information Technology**

- Implement widely accessible, affordable and validated mobile technologies for primary prevention into health systems for use by health professionals and lay people.
- Reframe risk categories. In communicating absolute stroke/CVD risk, categorising people into low, moderate and high risk should be abandoned. People with 10-year absolute CVD risk less than 30% should be motivated and taught by their health professional to control their modifiable risk factors and reduce their risk of stroke/CVD to as low as possible level.

**Early Life Interventions**

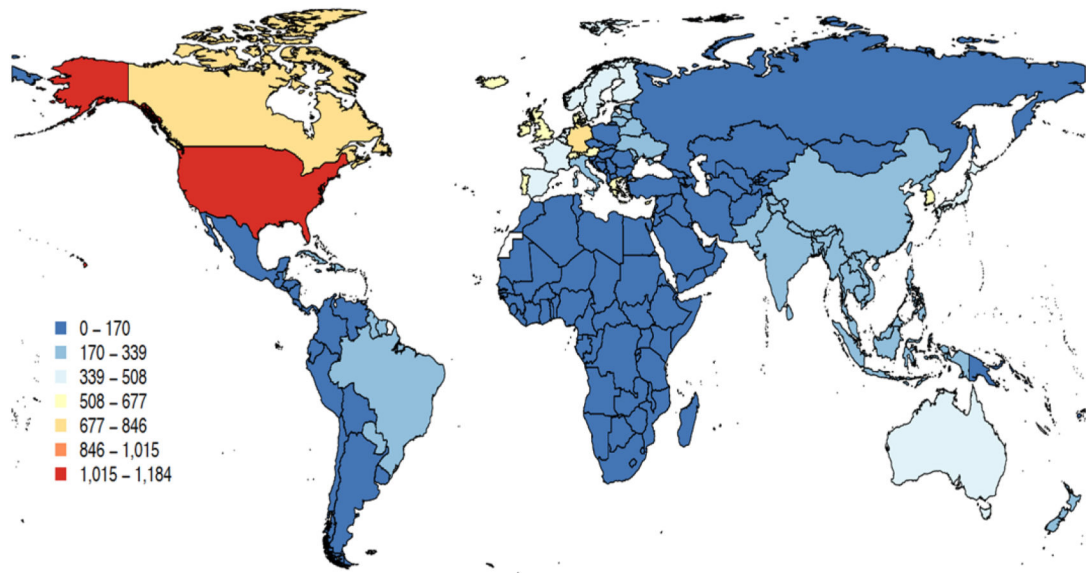
- Implement early-in-life culturally appropriate education about healthy lifestyle into standard education curricula with reinforcement across the lifespan



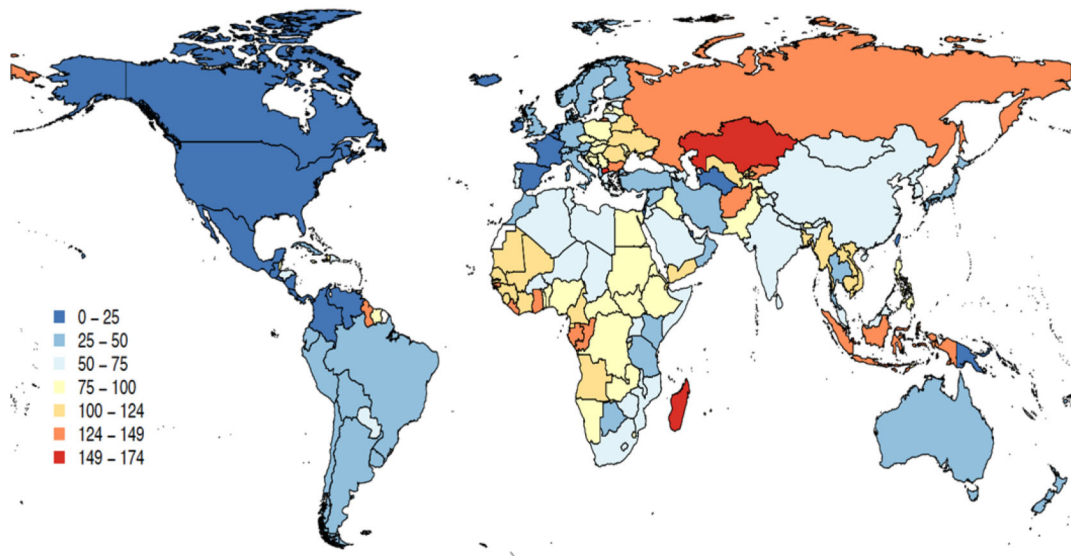
### KEY MESSAGES

- Although stroke incidence and mortality rates in the world declined from 1990 to 2013, in terms of absolute number of people affected by stroke, remained disabled or die from stroke the burden of stroke continues increasing at past pace throughout the world
- Ever-increasing burden of stroke across the globe suggests that currently used stroke and cardiovascular disease primary prevention strategies are not sufficiently effective
- For primary stroke prevention strategies to be more effective they need to be based on both population-wide and high risk prevention strategies, with the emphasis shifted from high stroke/CVD absolute risk approach to a more comprehensive approach that includes primary stroke prevention strategies in people with all levels of risk of CVD events
- To be cost-effective, primary stroke prevention strategies must be integrated with primary prevention strategies of other major non-communicable diseases that share common risk factors with stroke, such as CVD, vascular dementia, and diabetes mellitus
- Given the already immense and fast increasing burden of stroke and other major NCDs across all countries in the world that threatens sustainability of the whole society, not acting now on primary prevention of these diseases is not acceptable

### Age-standardized prevalence (per 100,000) of ischemic stroke in 2013

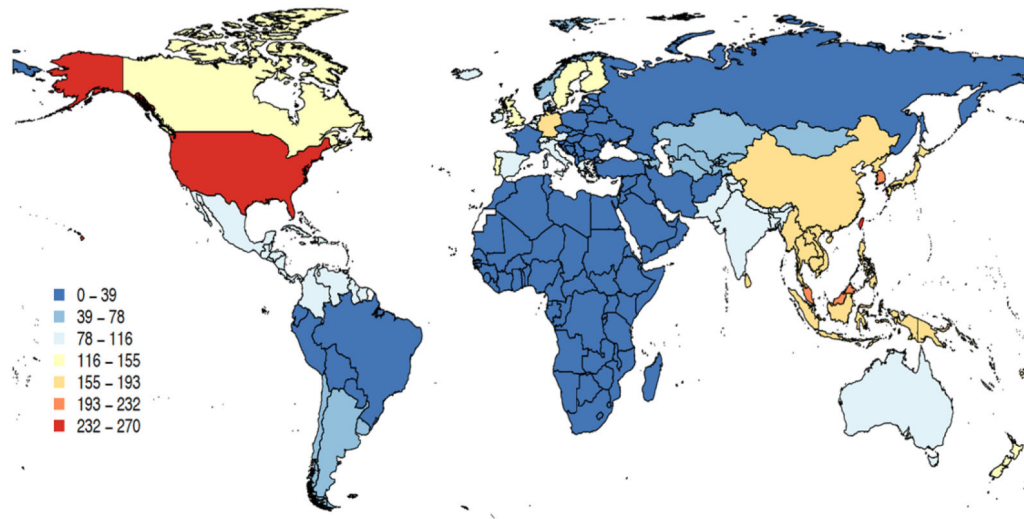


### Age-standardized death rate (per 100,000) of ischemic stroke in 2013

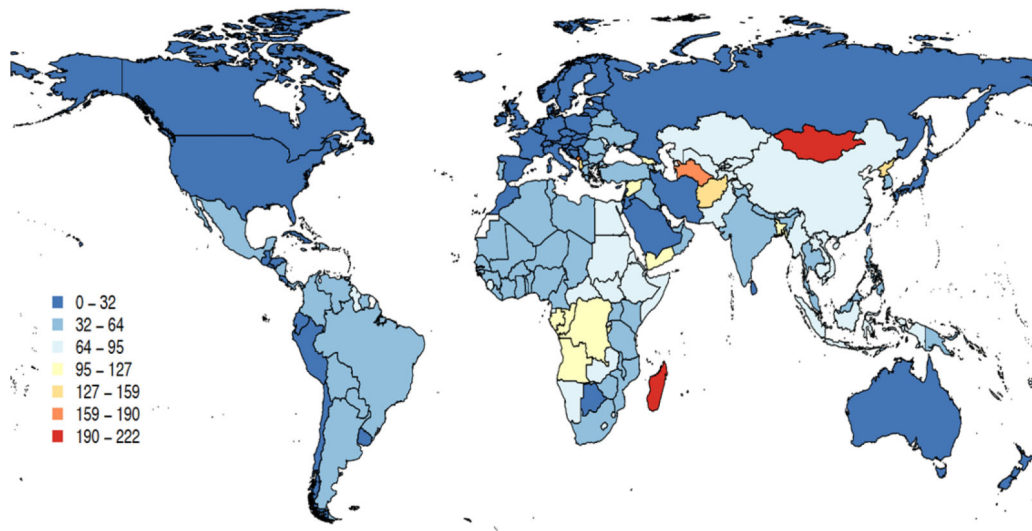


**Figure 1.** Age-standardised prevalence and mortality of ischaemic stroke per 100,000 person-years in various regions in 2013

Age-standardized prevalence (per 100,000) of hemorrhagic stroke in 2013



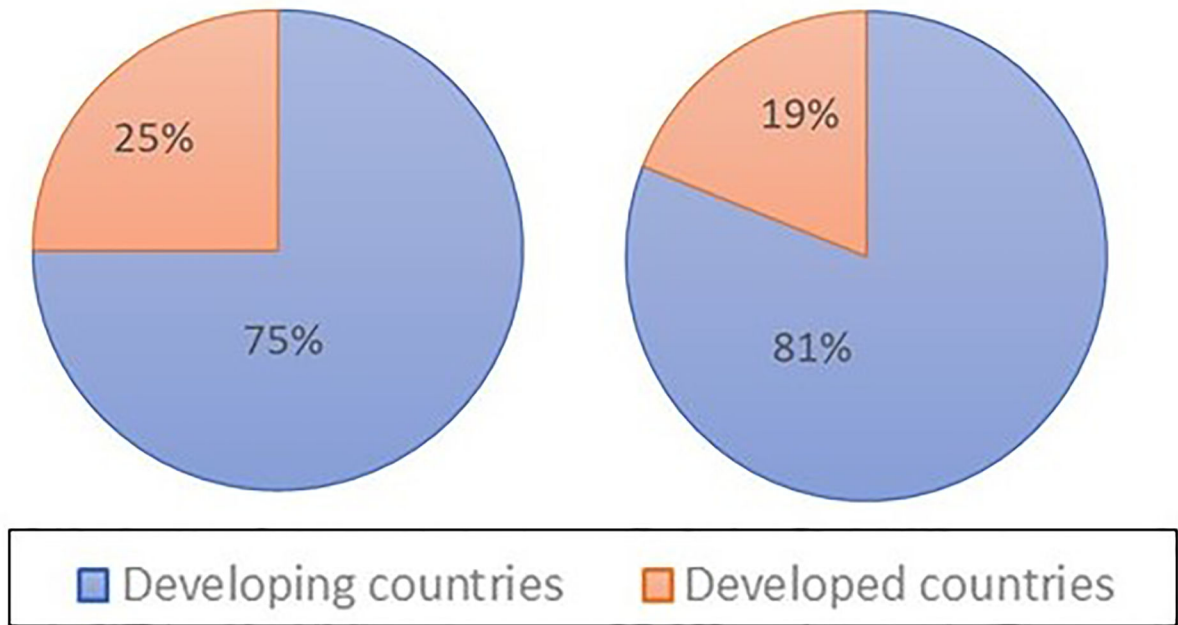
Age-standardized death rate (per 100,000) of hemorrhagic stroke in 2013



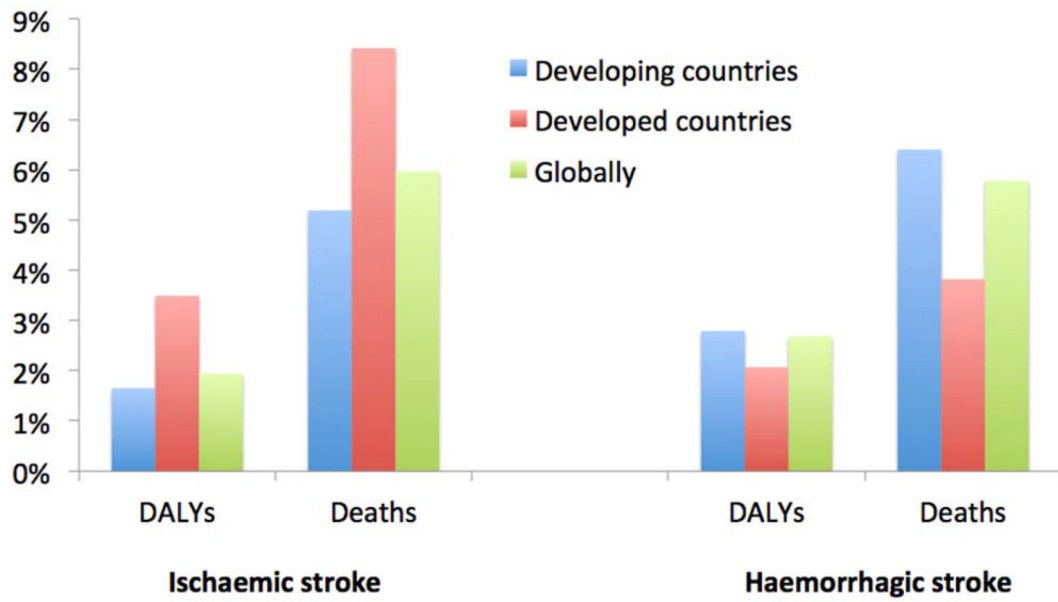
**Figure 2.** Age-standardised prevalence and mortality of haemorrhagic stroke per 100,000 person-years in various regions in 2013

a 6.45 million stroke-related deaths globally

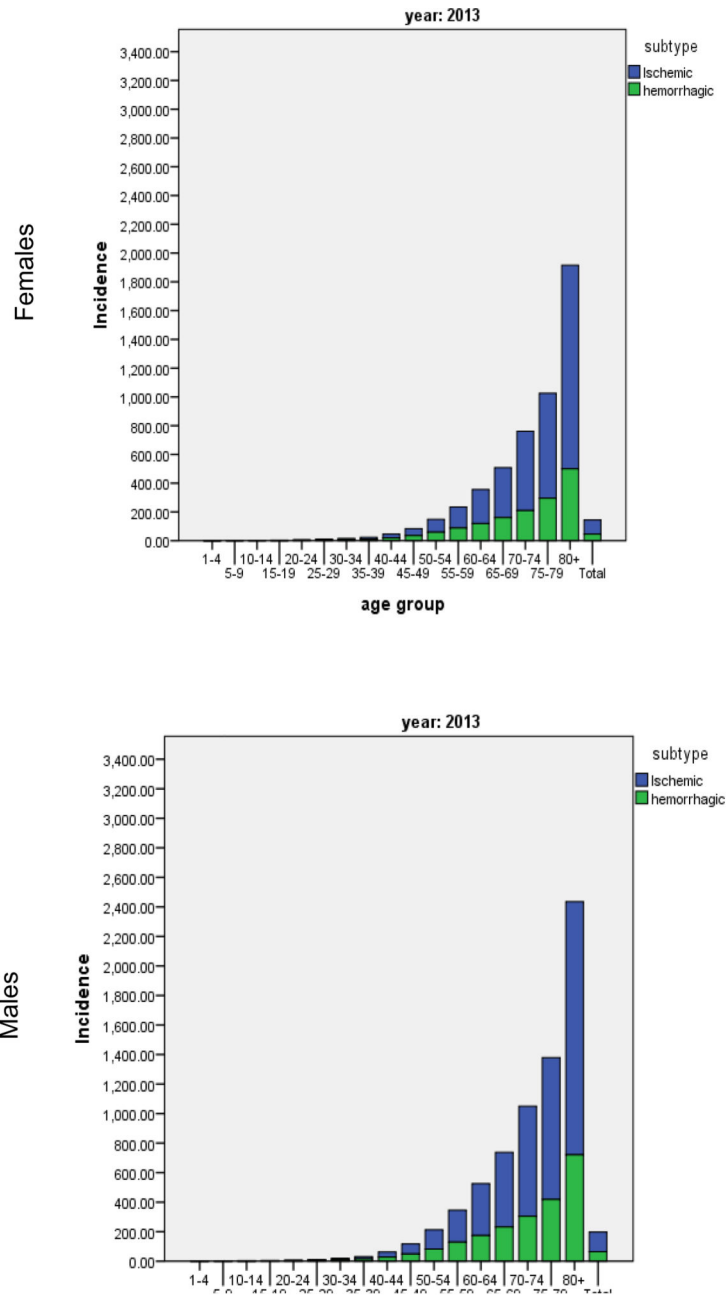
b 112.9 million stroke-related DALYs globally



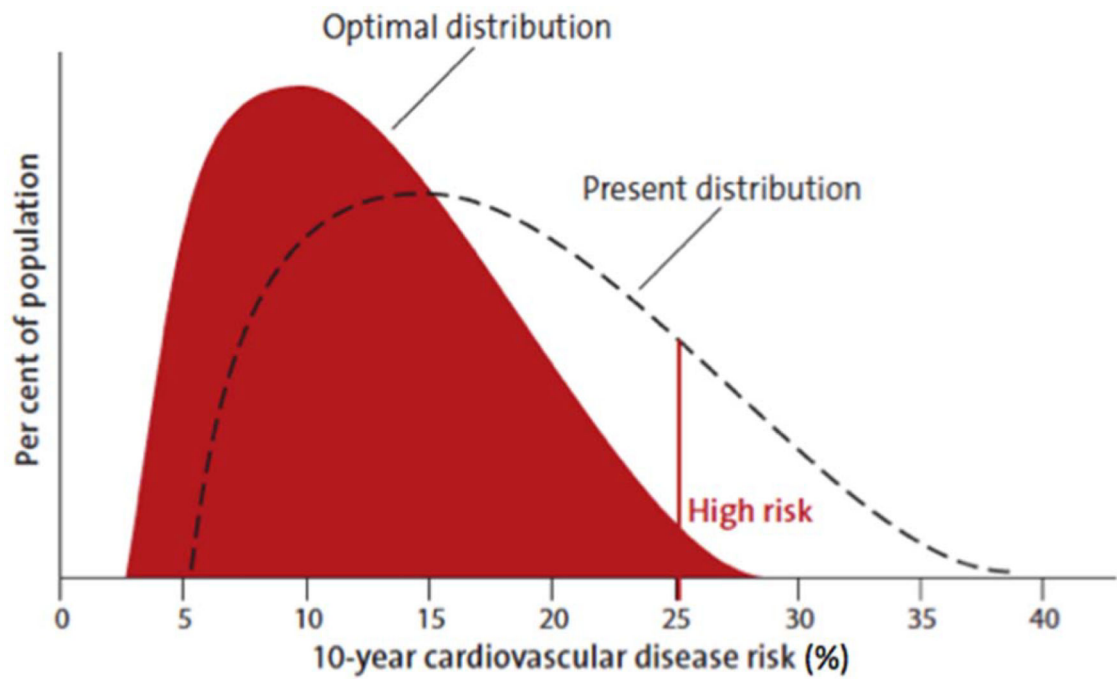
**Figure 3:** Stroke-related deaths and DALYs by country development status.



**Figure 4.** Proportional (%) contribution of ischaemic and haemorrhagic strokes burden (with 95% uncertainty intervals [UI]) to all health conditions by country development status in 2013 (modified from Feigin et al.)<sup>3</sup>



**Figure 5.** Incidence per 100,000 of ischemic and haemorrhagic stroke in females and males by 5-year age bands in 2013 (modified from S Barker-Collo et al.)<sup>10</sup>



**Figure 6.** Optimal shift in the distribution of CVD risk by combination of population-wide and high-risk prevention strategies (modified from WHO “Cardiovascular disease prevention. Translating evidence into action”.<sup>19)</sup>