SUMMARY

NUS Saw Swee Hock School of Public Health
Public Health Thought Leadership Dialogue:
Capturing the Value of Prevention
Tuesday, 17 May 2016, 2:00PM to 3:30PM

Not everything purported to be preventive works

Prevention can be a cornerstone in reducing the burden of disease globally and in enhancing wellness and overall well-being of individuals and communities. However, not everything "preventive" works and some approaches may be low-yield. We need to be guided by good scientific evidence in our actions. For example, only four screening processes showed strong evidence for reducing cause-specific mortality in randomised trials and almost no screening procedure showed unequivocal reduction in all-cause mortality. After a century of research in screening and years of screening activities for disease prevention, it has not delivered the expected outcome - the annihilation of diseases.

Main ways of capturing the value of an intervention

The main ways of studying the value of a preventive intervention are anecdotal evidence, observational evidence, randomised evidence, hybrid design and meta-analysis.

Problems with observational studies

1. Questionable reliability

a. Conclusions are fragmented:

This was illustrated by Dr JD Schoenfeld and Prof Ioannidis[1] when they examined studies in nutritional epidemiology through a systematic review of the literature on 50 ingredients that were randomly selected from a popular cookbook to see which ones were associated with increased or decreased risks of cancer. Forty of the 50 ingredients were linked to increased *and* decreased risks of cancer; evidence was found for both conclusions.[2] Furthermore, it is uncertain if the relative risks associated with each ingredient accurately reflected reality. Most of the ingredients would have some effect on cancer risks but there was no way to tell what a reasonable relative risk per serving per day might be. For instance, a particular fruit may be linked to decreased cancer risk but it was not shown how the risk changes with each increased intake of serving over time. The question remains on how to measure relative risks of single factors that are small but have significant relative risks when taken cumulatively.

[1] Schoenfeld JD, Ioannidis JPA. Is everything we eat associated with cancer? A systematic cookbook review. *The American journal of clinical nutrition*. 2013;2012;97:127.

[2] The search was conducted using the name of the ingredients instead of their biochemical content (e.g. "vanilla" instead of "vanillin"); this would explain the reason why minimal literature was found for the other 10 ingredients.

b. Selective reporting in published studies:
Dr Schoenfeld and Prof Inoannidis also found that, in the studies referred to above, those with significant findings were more likely to be published in study abstracts than those with nonsignificant findings, and meta-analyses would show smaller effect sizes than those reported in single studies. Most highly cited studies show stronger effects than subsequent studies[3]. It seemed like there was selective reporting and the imbalance in the number of published studies in favour of those with significant findings called to question the reliability of what was found in the literature.

2. Questionable effectiveness

a. Poor replication record:
Efforts using randomised trials to replicate the effects reported in observational studies have not been encouraging. Five out of the six most cited claims of observational studies were refuted within a decade[4] and in a study of 52 major epidemiological claims, none was validated in randomised trials[5]. There is also poor replication record for observational claims and for claims that take a long time from the initial description of the intervention to the cited article[6].

b. Incomplete picture:
Traditional observational studies only look at single or few factors and posit a causal relationship independent of all other factors the participants are exposed to; when in reality individuals are exposed to and are affected by a multitude of environmental factors. Further, it was shown that there can be significant correlation among a majority of these factors/variables[7], such that it is often impossible to tell if a factor is a cause, an effect, both, or just a correlate.

c. "Dangers" of big data[8]:
Big data is a potential boon to public health researchers, offering them the opportunity to analyse large volumes of complex data in many ways. However, having a massive amount of data increases the chance of reporting false positives, finding associations where there is none. It also increases the likelihood of positing patterns where there is none, increasing the temptation for researchers to pursue "problems" that would have previously been considered insignificant.

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[3] Ioannidis JPA. Contradicted and Initially Stronger Effects in Highly Cited Clinical Research. *JAMA*. 2005;294:218-228.
[4] Ioannidis JPA. *JAMA*. 2005.
[5] Young SS, Karr A. Deming, Data and Observational Studies. *Significance*. 2011;8:116-120.
[6] Contopoulos-Ioannidis DG, Alexiou GA, Gouvias TC, Ioannidis JPA. Medicine. Life cycle of translational research for medical interventions. *Science (New York, N.Y.)*. 2008;321:1298.
[7] A study of the correlation pattern between different nongenetic variables in the Singapore Prospective Cohort 2 showed significant correlation between a majority of the variables – illustrated as a dense web of correlation. ohn P. A. Ioannidis, Loy EY, Poulton R, Chia KS. Researching Genetic Versus Nongenetic Determinants of Disease: A Comparison and Proposed Unification. *Science Translational Medicine*. 2009;1:7ps8.
[8] Khoury MJ, Ioannidis JPA. Medicine. Big data meets public health. *Science (New York, N.Y.)*. 2014;346:1054.

Problems with randomised-controlled trials (RCT)
Currently, there exist large numbers of RCTs on non-regulated lifestyle interventions. However, these are fragmented and lack the quality control that is seen in clinical RCTs. Most of them are looking at outcomes of little impact and a majority lack evidence of the surrogacy of the outcome they are studying.

Hybrid of observational study and RCT
One way to overcome the limitations in observational studies and RCTs is to combine them and harness the strengths of each, by nesting randomised trials of lifestyle interventions within large cohort studies in a Multi-LIFE (lifestyle factorial experimental) design.[9] Participants in a cohort may choose a few lifestyle interventions from a laundry list and track the outcomes.

1. Generating the laundry list of lifestyle interventions

Efforts should be made to engage the community to find out what the community thinks constitutes "living well". This helps researchers develop the laundry list of randomised interventions. There is also the need to look at the various "literacies" for living well such as literacies in health, civic issues, transport, technology, finance and food. These literacies may even affect each other, impact disease outcomes or change how people live their daily lives.

2. Adherence by participants

A key challenge faced by traditional RCT study designs is the maintenance of participants' adherence to the programme. People often find it difficult to stick to the interventions assigned to them and returning for follow-up is usually a challenge. In order to overcome this, studies should be designed with a pragmatic trial range – to make it easier for participants by weaving the interventions as part of their daily routines. Also, inviting participants to be part of shaping their trial (e.g. selecting which interventions they would like to implement), increases the sense of ownership and self-motivation to comply. This will attract participation of the most motivated people. Admittedly there is the potential of selection bias, attracting a sample of only the ones who are most health-conscious and likely to adopt the intervention in the first place. However, this selection bias reflects real-life effectiveness of the intervention.

3. False negatives and false positives

False negatives are not a concern because of the large sample size, provided that the attrition and non-participation numbers are small. False positives may occur due to chance; researchers can check for false positives by replicating the outcomes across different cohorts and biobanks. Also, the issue of selective reporting by participants is less of a concern with a transparent cohort or biobank than it is with traditional RCTs.

4. Selection of outcomes

[9] Ioannidis JPA, Adami H. Nested Randomized Trials in Large Cohorts and Biobanks: Studying the Health Effects of Lifestyle Factors. *Epidemiology*. 2008;19:75-82.

Studies should focus on the outcomes that matter to people. Researchers should engage citizens to understand what is important for them in order to live a better life (e.g. experiencing empathy, compassion, fulfilment, etc.) For the selection of disease outcomes, researchers should look at the disease registries that are linked to biobanks or cohorts.

5. Trial Cost

Typically, a data-intensive trial with a randomised cohort of about 10,000 will cost about US$210m for a follow-up of four years. Simplifying the data collection method can potentially reduce costs by up to 90% and allow multiple studies to be run for the same cost. This can be done by leveraging information technology like the internet. In fact, one can argue that it is possible to randomise a cohort at zero cost as demonstrated by Google. Costs can be dramatically decreased further if there are already cohorts or registries in place.

6. "Citizen scientists"

Part of the effectiveness of multi-LIFE studies with nested randomised trials results from the engagement from the community in a large part of the process. Participants are no longer seen as passive study subjects but are actively involved as "citizen scientists". They can provide inputs on what interventions are being studied and they tailor their own trials according to what interests them. Such a design may be more attractive to people now that societies are more conscious of health and wellness.

7. Wellness

Wellness is not the same as an absence of disease, neither is it "health". Wellness goes beyond the physical dimension and extends to the spiritual, social, psychological and emotional aspects of being. It includes but is not limited to physical vitality, mental alacrity, social wellbeing and personal fulfilment. The wellness level of a person who is ill and dying may still be high even though his/her health level is low, and the wellness level of a person who is not ill may be low even though his/her health level is high. That being said, wellness and health are complementary but there is a need to move away from the traditional focus on health to look more at wellness.

8. Stanford University's Wellness Living Laboratory

All the above elements are incorporated in Stanford University's Wellness Living Laboratory (WELL) set to involve a sample size of tens of thousands. It now has 30,000 citizen scientists from three countries. The three components of WELL are i) an online registry where citizen scientists contribute information on wellness and other data; this registry can also be linked with other databanks that are available on the participants; ii) lifestyle interventions for citizen scientists to choose from and implement; and iii) a biobank that focuses on wellness outcomes and understand the biomarkers of wellness.

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Panel Discussion

Moderator: Prof Lee Hin Peng, LIGHT, SSHSPH

Panel:
1. Prof James Best, Dean, Lee Kong Chian School of Medicine
2. Dr Derrick Heng, Group Director, Public Health Group, MOH Singapore
3. A/P Rob M. van Dam, Domain Leader, Epidemiology Domain, SSHSPH

Prof James Best:
In some instances, there is strong evidence linking lifestyle with disease; diabetes, cardiovascular diseases and cancer have strong links with nutrition and physical activity.

There can also be links between the elements of wellness (e.g. psychological wellbeing and fulfilment) to health. There is much anecdotal evidence for this; it is not uncommon to hear of people's health deteriorating after retirement or the death of a spouse, or the positive impact pets or social connectivity can have on people's health, or the links between socialisation and mortality.

Seeing that there are numerous factors impacting an individual and that these factors are interconnected, selecting a single or a few factors to look at (which is currently the case in most studies) makes little sense. It is far better to study factors as a package and develop packages of interventions.

Some issues to consider are:
i. How do we change behaviour (dietary habits and physical activity) and have impact on feelings about life and social connectivity?
ii. What are the roles and responsibilities of the government, community and individuals in effecting these changes, and how do we balance these?
iii. How can individuals be helped to effect the necessary changes?
iv. It is not just the responsibility of healthcare agencies but a whole-of-government responsibility to provide citizens with the support to take responsibility and make the lifestyle changes.

Prof John Ioannidis:
There is a need to come to a consensus on what is important to the society. Health and mortality are still important. However, there are other aspects of life that are just as important but less tangible – these may not extend mortality but are still worth looking into because they impact the wellness of individuals.

Dr Derrick Heng:
In many cases, individuals know what they need to change in order to enjoy the positive outcomes (in wellness and health) that they desire. The issue is that they do not act on what they already know. Hence it is of interest to policy-makers and governments to understand what interventions are needed at the systemic and environmental levels to effect individual behavioral change. A related question is how RCTs can be conducted to study environmental changes. Governments are also interested in improving capabilities to evaluate programmes and capture the value of interventions. Finally, there remains the issue of how interventions can benefit the

least motivated people; there is decreased representatativeness in RCTs because the participants are usually the more motivated segment of the population.

Prof John Ioannidis:
A key thing for governments to decide is the amount of feedback it will need in order determine whether an intervention works. It is also important to select the reference indices carefully as some can be very information while some can be of little use though they contain a lot of data.

A/P Rob M. van Dam:
In the field of nutrition, consistent results have been reported across multiple large sample studies. Even so, it is unclear how effective the interventions will be in real-life since people tend to return to their usual dietary habits after some time. "Nutrition" is also a field where strong evidence-based recommendations are needed. So far, there have been strong cases made for some interventions as in the case of folic acid's link to the prevention of birth abnormalities.

Prof John Ioannidis:
The significance of the results in trials are not indicative of their success - trials that report significant results are not necessarily successful and trials that repeatedly show negative results are not necessarily unsuccessful. In fact, large long term trials that repeatedly show negative results can inform researchers on which ideas to forgo which ones to pursue. There is a need for more large-scale studies that will more accurately capture the effectiveness of an intervention. Regardless of what is reported in the laboratory on the chemistry of particular substance and their biological effects, there is still a need for trials that are designed to study the real life impact of such findings. Studies on interventions that people can practically implement and stick with are better than laboratory studies on biology or chemistry that do not translate to real-life benefits.