Where are the world’s disease patterns heading?
The challenges of epidemiological transition

Ailiana Santosa
Your life is a story of transition.
You are leaving one chapter behind,
while moving on to the next.
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ABSTRACT

INTRODUCTION: Epidemiological transition theory, first postulated by Omran in 1971, provides a useful framework for understanding cause-specific mortality changes and may contribute usefully to predictions about cause-specific mortality. However, understandings of mortality transitions and associated epidemiological changes remain poorly defined for public health practitioners due to lack of evidence from low- and middle-income countries. Therefore, understanding of the concept and development of epidemiological transition theory as well as population burden of premature mortality attributable to risk factors are needed.

OBJECTIVES: This thesis aims to understand how epidemiological transition theory has been applied in different contexts, using available evidence on mortality transitions from high, middle- and low- income countries, as well as the contribution of risk factors to mortality transitions, particularly for premature mortality.

METHODS: A Medline literature search from 1971 to 2010 was conducted to synthesise published evidence on mortality transition (paper I). A descriptive analysis of trends in cause of death using INDEPTH data was conducted, focusing on specific causes of death in 12 INDEPTH sites in Africa and Asia, using the INDEPTH 2013 standard population structure for appropriate comparisons across sites (paper II). A retrospective dynamic cohort database was constructed from Swedish population registers for the age range 30-69 years during 1991-2006, to measure reductions in premature non-communicable disease mortality using a life table method (paper III). Prospective cohort data from Västerbotten Intervention Programme from 1990 to 2006 were used to measure the magnitude of premature non-communicable disease mortality reductions associated with risk factor changes for each period of time (paper IV).

FINDINGS: There were changes in emphasis in research on epidemiological transition over the four decades from 1971 to 2010, from cause of death to wide-ranging aspects of the determinants of mortality with increasing research interests in low-and middle-income countries, with some unconsidered aspects of social determinants contributing to deviations from classic theoretical pathways. Mortality rates declined in most sites, with the annual reductions in premature adult mortality varied across INDEPTH sites, Sweden, which now is at late stage of epidemiological transition stage, achieved a 25% reduction in premature mortality during 1991-2006. Overall downward trends in risk factors have helped to reduce premature mortality in the population of Västerbotten County, but some benefits were offset by other increasing risks. The largest mortality changes accrued from reductions in smoking, hypertension and hypercholesterolaemia.

CONCLUSIONS: This thesis established patterns of current epidemiological transition in high, middle-and low-income countries (Asia and Africa), where the theory fits the transition patterns in some countries, but with some needs for further adjustments in other settings, as well as deviations from the classical ET theory in the last four decades. It highlights the need to identify the burden of mortality and morbidity, particularly for reducing mortality occurring before the age of 70 years and its attribution to risk factors, which are a major public health challenge. This informs shifting of public health priorities and resources towards prevention and control of chronic non-communicable disease risk factors.

KEYWORDS: epidemiological transition; premature mortality; non-communicable disease; risk factors; Sweden; low-and middle-income countries; INDEPTH Network; Västerbotten Intervention Programme.
LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, referred to as Papers I-IV


II. Santosa A, Byass P. Diverse empirical evidence on epidemiological transition in low- and middle-income countries: population-based findings from INDEPTH Network data. (submitted)


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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALC</td>
<td>Ageing and Living Conditions</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CSMFs</td>
<td>Cause-Specific Mortality Fractions</td>
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<td>CSMRs</td>
<td>Cause-Specific Mortality Rates</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>DALYs</td>
<td>Disability-Adjusted Life Year</td>
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<td>ET</td>
<td>Epidemiological Transition</td>
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<td>GBD</td>
<td>Global Burden of Disease study</td>
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<td>HDIs</td>
<td>Human Development Indices</td>
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<tr>
<td>HDSS</td>
<td>Health and Demographic Surveillance System</td>
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<tr>
<td>HIV/AIDS</td>
<td>Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>INDEPTH</td>
<td>International Network for the Demographic Evaluation of Populations and their Health</td>
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<tr>
<td>LMICs</td>
<td>Low-and Middle-Income Countries</td>
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<tr>
<td>MMR</td>
<td>Mortality Rate Ratio</td>
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<tr>
<td>MONICA</td>
<td>MONItoring of trends and determinants in CArdiovascular disease</td>
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<tr>
<td>NCDs</td>
<td>Non-Communicable Diseases</td>
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<tr>
<td>PAR</td>
<td>Population Attributable Risk</td>
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<td>RR</td>
<td>Relative Risk</td>
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<tr>
<td>SAGE</td>
<td>Study on global AGEing and adult health</td>
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<td>VA</td>
<td>Verbal Autopsy</td>
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<td>VIP</td>
<td>Västerbotten Intervention Program</td>
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<tr>
<td>WHA</td>
<td>World Health Assembly</td>
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INTRODUCTION

1. Epidemiological Transition Theory

Conceptual and development framework of Epidemiological Transition theory

The concepts of epidemiology and transition combine in a special way to define “epidemiological transition”. Epidemiology itself is the study of the distribution of disease and death, with their determinants and consequences, in population groups (1). The word transition comes from Latin, “transire”, defined as a story of movement from something through something and to something, a process occurring over time, involving development, which can be divided into stages, involving changes as a part of its nature, identified by complexity and multiplicity. The concept of “transition” has been used to explain dynamics in general and identified with different prefixes depending on disciplinary perspectives. Longitudinal studies and panel studies are needed to further explain and identify the dynamic process of transition (2).

The Epidemiological Transition (ET) concept developed by Omran emphasised the demographic, biological, sociological, economic and psychological consequences of transitional processes. Thompson, who worked initially with the concept of demographic transition in 1929, described how societies, originally with high mortality and high birth rates, over time transform into ones with decreasing mortality, followed by decreasing birth rate (3). Later, Landry introduced the phrase “demographic transition” in describing secular changes in fertility and mortality in 1934, which was reprinted later in England (4). Demographic transition, which is seen as a result of growing economies and industrialisation, mainly involves mortality and fertility transitions and their consequences for population changes. Recognising the limitation of demographic transition theory and of the need for comprehensive approaches to population dynamics, Omran introduced the notion of epidemiological transition in 1971. He described the changes in health, occurring during the demographic transition, where the largest burden of disease gradually shifts from infectious diseases to chronic, non-communicable diseases (NCDs). The term ET refers to the shift in cause-of-death patterns that comes with an overall decline in death rates, which provide a model for integrating epidemiology with demographic changes in human populations (5). The complex change in patterns of health and disease and their interactions with demographic and economic changes reflected historical experiences of populations in Europe and North America from the last half of 18th century to the 20th century.

Omran formulated five propositions of major importance for transition: (i) Mortality is fundamental for the dynamic of population growth; (ii) During the transition, a shift occurs in mortality and disease patterns whereby infections gradually are replaced by degenerative and man-made diseases in adults, towards dominance of the latter in the older people; (iii) During the epidemiological transition, the most obvious changes in health and disease patterns were among
children and younger mothers, resulting in declines of mortality and birth rate; (iv) Epidemiological transition in health and disease is therefore closely associated with the demographic and socio-economic transition, and with changes in life-style and modernisation; (v) Variations in the speed by which these changes occur, can be demonstrated in three basic models (i) the classical Western model (presented by western European countries), (ii) the delayed model (represented by most developing countries in Latin America, Africa, and Asia), and (iii) an accelerated model (represented by Japan) (5).

In his second proposition, Omran defines three stages of epidemiological transition (5):

- **Stage 1**: "The Age of Pestilence and Famine", a stage when mortality is high and fluctuating with predominance of infectious disease, thus precluding sustained population growth. Average life expectancy at birth is low and variable, in the range of 20 to 40 years.
- **Stage 2**: "The Age of Receding Pandemics", a stage when mortality declines progressively, accompanied with early decline of infectious disease, and the rate of decline accelerates as epidemic peaks become less frequent or disappear. The average life expectancy at birth increases steadily from about 30 to 50 years. Population growth is sustained and begins to describe an exponential curve.
- **Stage 3**: "The Age of Degenerative and Man-Made Diseases", a stage when mortality continues to decline and eventually approaches stability at a relatively low level. The average life expectancy at birth rises gradually until it exceeds 50 years. The major cause of death is degenerative disease.

In 1983, Omran recognised the necessity to renew his theory by extending more descriptions of the transition, based on critiques on emerging analyses of transition patterns and historical data which did not fit the original model (6). Later, Olshansky and Ault (7), followed by Rogers and Hackenberg (8), introduced the fourth stage of ET based on evidence of unexpected rapid decline from man-made disease (mainly from cardiovascular disease) in United States and some Western countries, labelled as “age of delayed degenerative death”. The cause-of-death patterns by age remain stable because deaths are postponed toward older ages and the relative incidence of degenerative causes of death, cardiovascular diseases, and cancers vary by age (7). The fifth stage of ET introduced by Olshansky and his colleagues, which is characterised by the emergence of new infectious diseases (HIV/AIDS, hepatitis B and C, Ebola) and re-emergence of former infectious diseases (cholera, malaria, diphtheria, tuberculosis, plague)(9). Omran agreed with those two additional stages added to his original theory of ET. He described the fourth stage as “the age of declining cerebrovascular mortality, ageing, lifestyle modifications and resurgent diseases”, a stage when life expectancy increased continuously (about 80-85 years), coincides with a decline and steady cardiovascular mortality due to improvement in medical health care and lifestyle changes, aside from emerging new infectious diseases and re-emerging former infectious diseases which he labelled as “the age of aspired quality of life, with paradoxical longevity and persistent inequities” (10).
Critiques of classical Epidemiological Transition theory

Many critiques referring to Omran’s ET model has been raised since its conception. The ET theory was criticised from the 1990s for being over-simplistic and not comprehensively describing the nature and chronological sequence of mortality transitions. The assumption that all countries will experience similar process of transitions with respect to onset and speed, which became known as a major critique of Omran’s theory, was not proven. In fact, not all countries have to deal with similar epidemiological transitions. Conclusions made by Omran based on historical mortality data from Sweden, England and Wales failed to understand the overall essence and sequence of mortality transition due to lack of a epidemiological evidence on the changing causes of patterns of diseases rather than changing causes of deaths. Mackenbach critiqued the ET theory as not distinguishing the beginning and the end of periods of transition (11). In addition, Frenk et al. (12) and Smallman-Raynor and Phillips (13) questioned the assumptions of ET theory, that ET is more likely to be a unidirectional structure in continuous development and not able to encapsulate the concepts of the protracted polarisation model of transition. Rather than focusing on the increasing burden of chronic disease, Frenk and Smallman-Raynor suggested broadening the orientation of ET theory towards population control in a global context. Ruzicka and Kane criticised a major assumption of ET theory, that societies will continuously experience significant decreases of infectious diseases without considering how changes in mortality trends relate to the changes in social determinants between and within societies. In fact, the observed variations in trends of mortality transition among population subgroups tended to increase health inequality problems resulting from heterogeneity within social class, and social-cultural, demographic and economic factors in general (14). Therefore, the generalisability of the ET theory has been doubted (15, 16).

The applicability and universality of ET theory across various places and contexts remain contentious (17-22). Carolina and Gustavo found paradoxical phenomena in the validity and interpretation of ET theory at the time the ET theory was used. They observed that ET theory has been used as phenomenological descriptions rather than theoretical explanations of changes in causes of deaths and diseases and their associations with the observed changes in societies, particularly in Mexico, and in low- and middle-income countries (LMICs) in general. Researchers often misinterpret ET theory, more or less taking the same perception as Omran described that the transition is uniform and follows a linear pattern (23). Omran argued that the framework of ET is not based on the demographic transition concept, and his theory was conceptualised to provide a wide-ranging approach to the observed processes of mortality and fertility changes over time. The changes in mortality patterns observed in developing countries, based on Omran's observations, were mainly due to national and international health programmes and environmental control, and not to economic growth (10).

However, later Omran's concept was questioned by McKeown and his colleagues, that changes in diseases and mortality trends from infectious disease to non-communicable disease observed in developed countries were mostly due to
improvements in nutrition and increased exposure to ‘conditions for which we are genetically ill-equipped’ (24). Preston stressed the weaker associations between economic growth and mortality changes occurred in countries with very low levels of income (25).

Gaylin and Kates determined the importance of morbidity and mortality differences between population subgroups, using the HIV/AIDS pandemic as a case study, and showed important inconsistencies with the optimistic, equitable trends implied by ET theory, suggesting that the modern picture may be more complex than the original theory could predict (16). The HIV/AIDS pandemic hit high-income (USA) as well as poor (African) societies, and unexpected falls in deaths from man-made diseases occurred, in particular cardiovascular disease (CVD) in some Western countries. Furthermore, there were unexpected falls in birth rates in spite of increasing mortality in many of the former Soviet republics, where public health systems collapsed, and even infectious diseases like diphtheria and tuberculosis re-emerged, propelled by increasing inequity, poverty, and tobacco and alcohol consumption. In 2004, Vallin and Mesle went through these convergences and divergences in death and disease, and arrived at a new approach to transition in health, acknowledging Omran’s model, and extending it (25).

Conceptually, the ET theory is a descriptive model and not an explanatory framework. The ET theory cannot be used either as a theory of general validity or as a technical tool for health policy and planning, especially in most environments of the developing world. This is the case especially in sub-Saharan African countries (25). One criticism of these ‘transition’ frameworks is their inflexibility in stipulating a stage-wise linear approach, treating the population as an undifferentiated unit and in an oversimplification of the transition patterns, which do not fit neatly into either historical periods or geographic locations (17). The theoretical construct of “epidemiological transition” due to Omran is a way of explaining population change, delineating the different development stages, which has lately been questioned for its assumptions that economic development is stage-wise and societies are subject to a natural destiny as well as measuring development by national averages and not accounting for social inequality (12).

Omran’s concept of the ET is situated at the convergence of the concept of the demographic transition, which preceded the concept of health transition. In addressing the conceptual drawbacks of the theory, an attempt to overcome the conceptual drawbacks of the model led a multidisciplinary group of authors to introduce the alternative term “health transition” that incorporated new elements into Omran’s theoretical assumptions (26). The term “health transition” was coined to incorporate new elements into Omran’s theoretical assumptions (17, 18, 21, 22). It was described as “a dynamic process whereby the health and disease patterns of a society evolve in diverse ways as a response to broader demographic, socio-economic, technological, political, cultural and biological changes” (27), and divided into ET (changes in health patterns) and health care transition (the organised response to health conditions).
2. Non-Communicable Disease and its Risk Factors

Taking a global view, all countries pass through different stages of epidemiological transition, a shift from predominant communicable diseases to non-communicable diseases. The recent Global Status Report on Non-communicable Disease 2014 showed that NCDs are the leading causes of death in the world, responsible for about two-thirds of total annual deaths (38 million deaths per year). The majority of premature NCD deaths (82%) occurred in LMICs. The largest proportion of NCD deaths was in South East Asia and Western Pacific (28). NCD mortality, including CVD, cancer, diabetes and chronic respiratory disease, increased most countries in the world. In contrast, the number of NCD deaths, particularly from CVD, decreased significantly in many high-income countries, due to improvement of health intervention programmes, adoption of healthier lifestyles and equitable provision of health services. In sub-Saharan Africa, NCDs are becoming a significant burden in terms of disease and mortality. WHO studies of burdens of disease predicted that the total annual number of NCD deaths would increase to 55 million by 2030, an increase of 37% in less than two decades. About 7 of 10 deaths worldwide will be due to NCD deaths, with the largest annual increase in NCD deaths due to CVD. Although NCDs have decreased in most high-income countries in the last few decades, the contrary is true in LMICs. The regions in the world predicted to face huge increases in NCD deaths are South East Asia (10.4 million), Western Pacific (12.3 million) and Africa (3.9 million), while European countries are projected to have minimal changes (29, 30). However, about 42% of all NCD deaths worldwide occurred before the age of 70 years (hence labelled as premature deaths). Of all NCD deaths, 28% and 48% occurred prematurely in high-income countries and LMICs, respectively, which should be avoidable. The proportion of premature NCD deaths was about three times higher in low-income countries compared to high-income countries, while the proportion for lower-middle-income countries was double that in high-income countries. Deaths from NCDs are still the leading cause for deaths under the age of 70, about 52% of total premature deaths, while communicable, maternal, perinatal and nutritional conditions accounted for 34% and only 14% were due to injuries. The proportions of global NCD deaths under the age of 70 in 2012 were CVD at 37%, followed by cancer (27%), chronic respiratory (8%), diabetes mellitus (4%) and other NCDs (23%) (28, 31).

Based on these facts, a call was made by the World Health Assembly (WHA) in 2012 aiming to reduce premature NCD deaths in the period 2010-2025 by 25%, hence labelled as the “25x25” target (32). The WHA resolution was reported in many contexts leaving out the critical word “premature”, which makes the target nonsensical in any setting where population ageing is occurring, and increasing numbers of elderly people encounter NCDs. The concept of “premature” NCD mortality was also not entirely clear in the original resolution (33). A clear definition was completed in the 2013 WHO Action Plan (34): a 25% relative reduction in the “unconditional probability of dying between ages of 30 and 70 from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases”. Subsequently, WHO established an NCD Global Monitoring Framework that provides guidance to monitor trends and assess progress made in the
implementation of strategies and plans on non-communicable diseases (35). The political declaration that was adopted by the WHA clearly stated that countries agreed to adopt nine global targets of premature mortality reduction on selected NCD risk factors: tobacco use, alcohol consumption, salt intake, obesity, raised blood pressure, raised blood glucose and diabetes, and physical inactivity, which are mostly preventable. Most NCD risks are the result of four behavioural risk factors (tobacco use, physical inactivity, unhealthy diet, and the harmful use of alcohol) that lead to four key metabolic risk factor changes (raised blood pressure, overweight/obesity, raised blood glucose and raised cholesterol). These risk factors are the leading causes of the death and disability burden in nearly all countries, regardless of economic development. The leading risk factors for mortality globally were raised blood pressure, followed by tobacco use, raised blood glucose, physical inactivity, and overweight and obesity (31).

A reduction in six NCD risk factors (tobacco use, alcohol consumption, salt intake, high blood pressure, obesity and diabetes) could prevent over 37 million deaths, with 16 million deaths prevented in people aged between 30 and 70 years, from the four main NCDs including cardiovascular diseases, chronic respiratory diseases, cancers and diabetes by 2025. Ezzati et al. estimated the number of deaths related to the four main NCDs that could be prevented between 2010 and 2025 by reducing the burden of each of the six risk factors to globally-agreed target levels. The targets include: a reduction of 30% in tobacco use with more ambitious target of 50% reduction; a 10% reduction of alcohol consumption, 30% reduction in salt intake, 25% reduction of high blood pressure, and halting the increase of obesity and diabetes prevalence. There would be a 22% reduction in premature deaths from CVD, cancer, diabetes, and chronic respiratory disease in men and a 19% reduction in women if countries achieved the goals set out by the “25x25” WHA. They estimated that the greatest benefit of reduction in premature deaths would be from reduction in tobacco use and high blood pressure (36). Although the WHA 25x25 target appears simple, the underlying epidemiology is complex. Countries would embark on the challenge in 2010 with very different disease patterns and health services, and strategies that might be good in some contexts for reducing NCD risks and mortality might not translate elsewhere. The target also paid no attention to previous trends in NCD mortality in particular countries (27). The comprehensive global monitoring framework with 25 indicators and nine voluntary global targets was set up in 2013 aiming to strengthen the national capability, multisectoral action and improving international collaboration to diminish risk factor’s exposure, strengthen health systems, and monitor the improvement in completing the global NCD targets.

The causes of NCDs are complex in nature as these diseases have multi-factorial causality. Several major social determinants of health factors are well known to be associated with the incidence of NCDs including physical environment, biological, behavioural and socio-economic factors (37). Age, sex and genetics, which are categorised as non-modifiable individual factors, together with behavioural risk factors, contribute to the development of NCDs. The major NCD risk factors are mainly in the avoidable category. Feasible and cost-effective interventions to reduce the burden and impact of NCDs exist. Continuous action to reduce risk factors and improve health care can prevent millions of
preventable premature deaths. Some of the behavioural risk factors associated with NCDs are closely interlinked to poverty, low education, poor diet, inequitable access to health services, and gender disparity. Men had a higher risk of death than women. The biological differences between men and women can influence the risk of premature death. For example, female hormones have a cardio-protective effect (38). Males tend to have central fat distributions that increase the risk of metabolic disease (39).

Modifiable (Behavioural) Risk Factors

a. Tobacco use

Tobacco use is one of the major risk factors associated with NCD deaths, which also shares with other modifiable risk factors such unhealthy diet, physical inactivity and alcohol consumption in increasing the risk of NCD deaths. About 6 million deaths are related to tobacco use every year in the world, which are more than 80% of deaths related to tobacco occur in LMICs. The prevalence of daily tobacco smoking varied widely among the six WHO regions in 2010, with a declining trend in the European Region and an increasing trend in the South East Asia Region. Men smoked more than women in the world, with the largest disparities for daily cigarette smoking being in the Western Pacific and South East Asia Regions (15 and 10 times higher in men than in women, respectively) (40). Tobacco use accounted for 12% of all deaths in men and 6% of all deaths in women. Tobacco use is projected to cause over 8 million deaths annually by 2030. Despite progress in reducing prevalence of daily smoking since 1980, the number of smokers has increased steadily worldwide, and there are preliminary indications that global prevalence among men increased in recent years (41).

In Sweden, proportion of daily smokers has decreased in men and women from 1985 to 2012, a decrease of 56.3% and 53.6%, respectively (42). Although smoking has declined in Sweden in the last four decades, still one in nine Swedish people are daily smokers now. Smoking is more common among women than men. Recent data from the Swedish National Public Health Report 2012 showed that about 13% of men and 15% of women were smokers. Compared to other European countries, Swedish men have the lowest tobacco-related mortality, while Swedish women were above the European average. Although the prevalence of smokers has declined in all age groups, the magnitude of decline varied across age groups. Younger men tended to stop tobacco smoking more than in older age groups. There is a shifting pattern of smoking observed in northern Sweden, from tobacco use to snus use, particularly among younger age groups (“snus” is a typically Scandinavian product, consisting of moist tobacco powder in small paper sachets which are placed in the mouth). The Västerbotten Intervention Programme (VIP) data showed that the proportion of smoking decreased in men and women aged 40, 50 and 60 years in Västerbotten County in Sweden during 1990-2007, a decline of 10% and 9%, respectively. However, smoking has not declined significantly among people with basic education, while use of snus continued to increase among this group (43).
b. Physical inactivity

Based on the WHO recommendation, physical activity levels are categorised into three groups: physical inactivity, moderate physical activity (if they do at least 150 minutes of moderate intensity aerobic physical activity throughout the week) and active physically (at least 75 minutes of vigorous intensity aerobic physical activity throughout the week or an equivalent combination of moderate and vigorous-intensity activity). Physical inactivity is recognised as one of the major modifiable risk factors for CVD, diabetes, and breast and colon cancer. Approximately 31% of the world’s population are physically inactive. Women were more likely to be inactive during their leisure time compared to men. The prevalence of physical inactivity also increased with national income levels. The prevalence of physical inactivity was double in high-income countries for both men and women (41% and 48%) compared with low-income countries (18% and 21%) (44). In Sweden, a survey conducted by the Swedish National Institute of Public Health during 2004-2011 showed that about 13% of men and 14% of women reported not exercising in their leisure time, with no significant change (45). The VIP data showed that the proportion of people engaging in intense physical activity increased among people aged 40, 50 and 60 years in Västerbotten County during 1990-2007, an increase of 8.2% in men and 17.8% in women. However, prevalence of physical inactivity persisted over the 18-year period, particularly among men and people with basic education (46). A multi-country MONICA study in selected sample of individuals aged 25-64 years who lived in Västerbotten and Norrbotten found that there was no change in physical inactivity prevalence among men and women aged 25-64 during 1990-2004 (47).

c. Unhealthy diet (fruit, vegetables, whole grain, nuts, seeds, fat and salt intakes)

Healthy diets, which consist of low dietary intakes of fat and salt, and high dietary intakes of fruits, vegetables, whole grains, nuts or seeds, can reduce the risk of developing CVD, stroke, chronic kidney disease, diabetes and cancer. The recent WHO report on NCD risk factors estimated about 1.5% to 4% of the global burden disease was attributable to high intakes of fat and salt and low intakes of fruits, vegetables, whole grains, seeds or nuts. About 2.7 million deaths were attributed to unhealthy diet, accounted for mostly by NCD deaths. The deaths attributed to unhealthy diet were projected to be about 19% of gastrointestinal cancer, 31% of coronary heart disease and 11% of stroke. A shift toward increased animal-source food intake and caloric sweeteners and decreased intakes of fruits, vegetables and grains was observed in LMICs (48). Some studies conducted in Mediterranean countries found an increasing trend in the intakes of high fat and high-calorie foods in these countries (49), in contrast to Nordic countries and some Southern European countries (50). Information about dietary intake in Sweden comes from the Public Health Survey conducted by the Swedish National Institute of Public Health in 2007–2010. It showed that women fulfil the food recommendation of intake of fruit and vegetables (five times a day or more, to a minimum of 500 g), twice as often as men (13% vs. 5%, respectively). Intakes of meat, vegetables, fruits and grains have increased among the Swedish population during 2007-2010, although it remains below the recommended amount of 500 g
per day. Although Swedish children have improved their eating habits during 2001-2005, they continue to consume excessive amounts of sweets and soft drinks (51).

d. Alcohol consumption

Alcohol consumption has immediate effects on diminished brain function, risk of unintentional injuries, risk of violence and death. Consuming alcohol for longer periods has long-term effects on liver diseases, cancer, hypertension, neurological and psychiatric problems. About 11.5% of all alcohol drinkers are categorised as heavy consumers. Alcohol consumption is responsible for about 2.7 million deaths every year in the world, and become the leading single risk factor for the disease burden particularly in Eastern Europe and Latin America. European countries have the highest proportion of premature death due to alcohol consumption, with the most heavy consumption drinkers in all age groups. According to the WHO country profile for alcohol consumption, about 23.8% of Swedes age 15 and over in 2010 consumed alcohol heavily (33.2% in men and 14.5% in women) (48). The effects of alcohol on population health have been observed to be greater in Russia and some other former Soviet republics, with about 33%-50% of total deaths in young and middle-aged men in Russia attributed to alcohol consumption (52).

Metabolic Risk Factors

a. Raised blood pressure

Raised blood pressure (hypertension) is the leading risk factor for CVD, particularly coronary heart disease, ischaemic heart disease and stroke. The proportion of raised blood pressure in adults aged 25 and over in the world increased from 26.4% in 2000 to 40% in 2008, with the highest prevalence of hypertension in Africa (46%), while in high-income countries, the prevalence of hypertension was about 35%. Mean systolic blood pressure varied significantly across countries, and overall it has not declined significantly. The highest mean systolic blood pressure was in LMICs. Overall, men had somewhat higher prevalence of hypertension than women (48). A study using data from the WHO Study on global AGEing and adult health (SAGE) found that the prevalence of hypertension among older people aged 50+ varied, with range from 32.3% in India to 77.9% in South Africa (53). The multi-country MONICA longitudinal study showed that the prevalence of hypertension decreased in both men and women populations during the 1980s and 1990s, with the largest decline being in eastern Finland. A modest decline was observed among men and women in northern Sweden (54). The latest WHO country profile on NCD risk factors showed that the proportion of raised blood pressure in Sweden in 2008 was 30.8% in total (34.9% in men and 26.8% in women) (48). The VIP data showed that the proportion of hypertension among people age 40,50 and 60 in Västerbotten County decreased significantly from 1990 to 2010, a decrease of 6.2% in men and 10.1% in women, with some geographical variations within the county (55).
b. Overweight/obesity

Obesity is an abnormal condition of excess body fat, which is calculated as a weight-for-height body mass index (BMI) in kg/m², with a BMI greater than or equal to 30 representing obesity. Obesity is a major risk factor for NCDs such as CVD, diabetes, musculoskeletal disorders (osteoarthritis) and specific cancers (breast, colon and endometrial). About 11% of men and 15% of women in the world were obese. The proportion of overweight was double in high-income countries compared to LMICs, with about 50% and 25% of adults being overweight and obese. In 2014, more than 1.9 million people aged 18+ years were overweight (a BMI greater than or equal to 25) and one third of those overweight people had BMI more than 30. The proportion of people overweight and obese is higher among women. The epidemic of excess weight is due to imbalance between dietary energy intake and physical activity, which markedly increases the risk of CVD, cancer, incidence of falls and psychiatric problems. Overall, prevalence of raised BMI increased globally along with increasing levels of national income. Prevalence of overweight and obesity increased significantly more in lower-income countries than high-income countries over the last few decades, an increase of 15-24% in lower-middle-income countries and 10-16% in low-income countries (48).

c. Raised blood glucose

In 2014, the global prevalence of diabetes among adults aged 18+ years was 9% (382 million), which has doubled from 1980 to 2014. About half of people with diabetes in South East Asia are undiagnosed. According to the latest edition of the International Diabetes Atlas, about 4.9 million deaths were related to diabetes, and more than 80% of deaths related to diabetes occurred in LMICs. European countries had the highest prevalence of type-1 diabetes in children. In Africa, premature death related to diabetes was approximately 76% of total deaths related to diabetes. The worldwide prevalence of diabetes is projected to increase from 2.8% in the year 2000 to 4.4% in 2030, an increase suggesting an on-going global epidemic of diabetes. Overall, the greatest increased prevalence of diabetes will be in sub-Saharan Africa, with an increase from 19.8 million in 2013 to 41.4 million in 2035. The next regions were the Middle East and North Africa, and South East Asia, with increases of 96% and 71% respectively. The emerging burden of diabetes is observed in the Middle East, Western Pacific, sub-Saharan Africa and South-East Asia, where economic growth has changed lifestyles. These rapid transitions are bringing previously unheard of rates of obesity and diabetes, which developing countries are facing huge burden of ill health with inadequate resources to protect their populations. The VIP data showed a significant increase of diabetes prevalence during 1990-2007 among people aged 40, 50 and 60 years (an increase of 44% in men and 17% in women). The older groups (aged 50 and 60) had higher risks of developing diabetes in a 10-year period compared to people age 40, while the risk of developing diabetes decreased significantly in women between 2000 and 2007, a reduction of 30% (56). A recent study conducted by Long et al. showed an upward shift in the population distribution of glucose concentrations with a significant increase in mean glucose. Despite the increase in blood glucose concentrations, the prevalence of diabetes in Sweden is lower than other European countries (57).
d. Raised total cholesterol

Raised total cholesterol (hypercholesterolaemia) is one of the leading causes of disease burden in the world that increases the risks of developing heart disease and stroke. The prevalence of raised total cholesterol increased remarkably according to the increasing level of national income. In 2008, about 37% of men and 40% of women raised their total cholesterol to more than 5.0 mmol/L, globally. A modest decline was observed during 1980-2008 with a decrease of total cholesterol of 0.1 mmol/L in every decade. The highest prevalence of hypercholesterolaemia was in Europe (54%), followed by the Americas (48%). Meanwhile South East Asia and Africa still ranked in the lowest place, about 29% and 22.6% respectively (48). Raised total cholesterol can be attributed to 4.5% of total deaths and 2% of total DALYs. A downward shift in the entire population distribution of cholesterol and blood pressure was observed among the middle-aged population of Västerbotten County, with significant decreases in mean age-adjusted cholesterol and SBP during 1990-2010 (58).

3. Non-Communicable Disease Mortality Attributable To Risk Factors

The recent WHO Global Report on NCDs showed that the leading global risks for mortality in the world are high blood pressure, responsible for 13% of deaths globally, tobacco use (9%), high blood glucose (6%), physical inactivity (6%), and overweight and obesity (5%). These risks are responsible for raising the risk of NCDs such as heart disease, cancer, diabetes and chronic respiratory disease. They affect countries across all income groups: high, middle and low. In high income countries, the three leading individual risks attributed to overall mortality and burden of disease were high blood pressure, smoking and high cholesterol (59). A prior cohort study in southern Sweden conducted by Nilsson et al. found that 49% and 32% prevalence of smoking and hypercholesterolaemia in men were attributed to 39% and 18% of coronary heart disease. By applying healthy diet, moderate or intense physical activity and avoiding tobacco use, they estimated 80% of premature CVD mortality, 80% of type 2 diabetes mortality and 40% of cancer mortality could be prevented (60).

Kontis et al. have estimated that decreasing exposure to six NCD risk factors globally could avert over 37 million deaths by 2025, a decrease of 43% in people ages of 30 and 70 and 57% in people aged 70+, compared to upward trends or stagnation in risk factors. If each country fulfils the NCD risk factor targets, the probability of dying from premature NCDs deaths will decline by 22% in men and by 19% in women by 2025. If there is no additional action on reducing the risk factor trends, the probability of dying from premature NCDs death will only decline by 10-11% in men and women. The most benefits of achieving the NCDs risk factor targets will be in LMICs (31 million deaths prevented) (61). However, few studies have demonstrated how changes in specific risk factors directly affect changes in mortality. Modelling studies from USA (62, 63), Finland (64), and the United Kingdom (65) partly attributed reductions in CVD mortality to changes in risk factors. The multi-country MONICA study, which included Sweden, found
that changes in risk factor exposure (based on prospective individual assessment) only partially accounted for observed reductions in coronary heart disease mortality, with the other major influence being improved medical treatment (47). However, the same study highlighted the difficulty of attributing risk factor exposure to CVD mortality. A population-based study in Switzerland examined relationships between NCD risk factors and mortality at older ages, but did not concentrate on the concept of premature NCD mortality (66).

Some evidences showed the attributable risk factors to NCD death. About 12% of all deaths among adults at ages of 30 and over were attributed to tobacco use. Of the four main components of NCD deaths, tobacco use was responsible for 10% of CVD mortality, 22% of cancer mortality, and 36% of chronic respiratory disease mortality. A longitudinal study conducted in southern Sweden showed that smoking was the main risk factor attributed to coronary heart disease (39%), followed by hypercholesterolaemia (18%) and diabetes (3%) in both men and women (60). Tobacco use was attributed to 71% of lung cancer mortality, 38% of ischaemic heart disease mortality and 41% of deaths related to chronic obstructive pulmonary disease. CVD deaths attributed to tobacco use were more likely to occur among younger adults. Reduction in tobacco use is estimated to reduce the probability of death of more than 24% in men and 20% in women. The number of deaths attributable to diabetes increased by 11% from 2011 to 2013, which was mainly due to increases in the Western Pacific and Middle East and North African regions. A multi-country population-based study conducted by Arnold et al. in 2012 showed that about 3.6% of all cancer in adults aged 30 and over was attributed to high BMI (5.4% in women and 1.9% in men). In addition, the attributable fractions were higher in countries with high Human Development Indices (HDIs) than countries with moderate or low HDIs (67). Ramström et al. found that Swedish men had the lowest level of mortality attributable to tobacco use in Europe, while Swedish women were at an equal level to the European average (68). Estimating the burden of disease attributable to risk factors has now become common practice within public health field in translating research findings into public policy, as well as providing the potential magnitude of the burden of disease that could be prevented through health prevention programmes.

4. Significance of the research area

Despite many criticisms that have been raised, ET theory has been used as an important conceptual framework for understanding disease and mortality pattern changes over time in the last few decades, from predominantly infectious diseases to chronic non-communicable diseases. Murray and colleagues showed that measuring the ratio of communicable diseases and NCDs can be used as an indicator of progress along the path of the ET (69). However, clear understanding of mortality transition and its implications is still hampered due to a lack of evidence and the availability of long-term population statistics particularly from LMICs (70) that makes it difficult to understand the generalisability of the theory globally, as well as its interpretation. Changes in disease classifications over time also limit the comparability of available data for assembling a comprehensive
global pattern of mortality transition (71). An overview of how the ET theory has been applied since its conception and the identification of gaps where it fails through empirical evidence and available data is needed. Therefore, we conducted a systematic review on the evidence of mortality transition in the last four decades (paper I).

Realising the lack of availability longitudinal health and demographic data in LMICs, INDEPTH Network has worked to bridge the gap in high quality population-based data, some of which was utilised for paper II. Since 1998, the INDEPTH Network has conducted continuous demographic surveillance system via sites that provide high quality, population-based, health and demographic data on a longitudinal basis, and created a critical resource of valid, population-based information for much of the developing world (72, 73).

There is no country that can ignore the present and future challenge posed by NCDs, including Sweden, although there are enormous differences existing in stages of ET across the world. Sweden has well-known experience in epidemiological transition since the 18th century, from predominantly communicable disease to non-communicable disease, as a part of economic growth and medical innovations. However, achieving a goal set by the WHO to achieve a 25% reduction in premature death from 2010 to 2025 is still a matter of speculation for Sweden, which has reached an advanced stage of ET in the last few decades. Using the unique and high quality individual Swedish national data, we tried to assess the achievement of premature mortality reduction over an earlier 15-year study period (paper III).

Although the recent Swedish National Public Health Report showed that Sweden achieved a significant decline in cardiovascular mortality in the last few decades, other components of NCD mortality such as cancer remained stable or increased due to poor life styles (42, 74). A plethora of global studies, which were mostly relying on estimation methods, have investigated how changes in specific risk factors directly affect changes in mortality. However, detailed assessments of how relevant individual risk factor exposures contribute to individual and population dynamics of premature mortality remain unclear (paper IV).

Therefore, the overall aim in this thesis was to understand how epidemiological theory has been applied in different contexts, using available evidence on mortality transition from high-, middle- and low- income countries, as well as the contribution of risk factors to mortality transition, particularly to premature mortality.
OBJECTIVES OF THE STUDIES

1. Overall Objective

To understand how epidemiological theory has been applied in different contexts, using available evidence on mortality transition from high-, middle- and low-income countries, as well as the contribution of risk factors to mortality transition, particularly to premature mortality.

2. Specific Objectives

Paper I aims to provide a general overview on how Omran’s ET theory has been used and challenged since its conception, and how it has been applied to understand population health transitions in high, middle- and low-income countries.

Paper II aims to examine trends in premature mortality in various categories cause of death in low- and middle-income countries (from INDEPTH Network sites across Africa and Asia), according to the WHO 2012 verbal autopsy (VA) cause categories, in the context of the epidemiological transition framework.

Paper III aims to assess whether a postulated target of a 25% reduction in the unconditional probability of dying between ages of 30 and 70 from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases from 2010 to 2025 might have already been achieved during an earlier equivalent time period (1991-2006) in Sweden, a late-transition and high-income country, using individual national data. Secondary objectives are to assess which population sub-groups were more or less successful in contributing to changes in premature NCD mortality, drawing lessons of global relevance for countries aiming to achieve 25% reductions in premature NCD mortality from 2010 to 2025.

Paper IV aims to attribute changing risk factor exposures to patterns of premature (age 40 to 70 years) non-communicable disease mortality in northern Sweden, using available individual risk factor and mortality data.
CONCEPTUAL FRAMEWORK

PROCESSES OF EPIDEMIOLOGICAL TRANSITION

Early stages
- Pestilence and Famine
- Receding pandemics
- Degenerative and Man-Made diseases
- Delayed Degenerative Infections

Late stages
- Birth rate
- Death rate

Papers:
- Paper I: Global evidences of epidemiological transition in the last four decades
- Paper II: Current evidences of epidemiological transition in low and middle-income countries
- Paper III: Premature mortality trend in high-income country
- Paper IV: Risk factor contribution to premature mortality in high-income country

Data sources:
- Systematic review
- INDEPTH data
- Swedish National data
- VIP data

TIME
METHODS

1. Study Settings and Data Sources

Global context – Systematic Review

We conducted a systematic review (paper I) using PubMed to synthesize the published evidence on mortality using selected keywords ‘epidemiological transition(s) or epidemiologic transition(s) or demographic transition(s) or health transition(s)’ and ‘mortality’. The inclusion criteria were articles only on human research and published in English from 1 January 1971 to 31 December 2013. A total of 547 articles were found, which were later screened by reading their titles and abstracts. From this step, a total of 324 articles were excluded (210 irrelevant papers and 114 reviews/commentaries/editorials). Review papers including Omran’s and Caldwell’s conceptual papers (5, 26) were excluded from the formal review but used to provide a framework for discussion. The full texts of the remaining 223 articles were searched and read through. We obtained 16 additional articles, not found in the original search, from the reference lists of relevant studies and review articles. We could not obtain full text for 29 papers. Therefore, a total of only 210 articles were included for full text review in the second step. All citations were saved in the PubMed database and imported into the EndNote X6 database. All full text articles were reviewed by two of the authors for inclusion in the study. Uncertainties over study inclusion were discussed between the researchers and resolved through consensus. Another 74 papers were further excluded after reading the full text, mainly because of insufficient mortality data (n=23), observational studies assessing risk factors and outcomes in a defined population (n=17), and papers not directly relevant (n=34). A final 136 articles were included in the review. Figure 1 shows the systematic review process and outcome for papers relating to Omran’s theory of epidemiological transition.

Low- and Middle-Income Countries - INDEPTH Network Data

The INDEPTH Network is an international network that coordinates Health and Demographic Surveillance System (HDSS) sites in low- and middle-income countries (LMICs). Established in 1998, it was designed to fill the lack of reliable population-based data on health in LMICs. The INDEPTH Network members consist of functional independent demographic and health research centres, which are conceptually based on self-selection of site locations in places where the reliable population-based data are lacking. Therefore, geographical distributions of these HDSS do not necessarily represent national situations or random population samples. In each HDSS, longitudinally based epidemiological data collection for risks, exposures and outcomes in a defined population were set up comprehensively. The INDEPTH Network now covers 52 HDSSs in 20 countries in Africa (39 HDSSs), Asia (11 HDSSs) and Oceania (2 HDSSs), consisting over 3,800,000 people under the surveillance. This population-based longitudinal study focused in LMICs created new chances for sharing and
exchanging health data between some of the world’s poorest countries, as well as being a platform for methodological development of new approaches to surveillance. The INDEPTH 2013 standard population was created to allow comparison between sites since the age-sex population structure varies across site and over time. The standard population has been compared to other global standards such as Segi and WHO due to different fertility and younger-age mortality rates frequently observed in LMIC populations (72, 73). The INDEPTH mortality data, which were used in paper II, were collected using verbal autopsy (VA) interviews by special trained interviewers. A probabilistic model, namely the InterVA-4 model, was used to assess likely cause(s) of death for each VA, based on a combined expert medical opinion and relevant available data on signs and symptoms of the deceased prior to the deaths.

Figure 1: Flow diagram of the systematic review process and outcomes for papers relating to Omran’s theory of epidemiological transition. Figure is reproduced from Global Health Action. 2014 (27).
The InterVA-4 model is the only model currently available to categorise causes of death according to the WHO 2012 standard. Because the VA data were collected before the WHO 2012 standard was formulated, a transformation of retrospective data into the WHO 2012 and the Inter-VA input format was required. For each verbal autopsy, the InterVA model assigns a maximum of three likely causes of deaths or an indeterminate conclusion. Where the likelihood of the assigned causes totalled less than 100%, the residue was assigned as indeterminate. In addition, the InterVA-4 model requires local settings for malaria and HIV/AIDS, based on local conditions (75). The appropriate malaria setting was “high” for all the West African sites and East African sites except in Nairobi, Kenya and “low” for other sites. The HIV/AIDS setting was “high” for sites in Kenya, Malawi and South Africa, while all other sites were grouped used the “low” HIV/AIDS setting.

Figure 2: Map showing locations of the 12 INDEPTH sites, with numbers of deaths registered, VAs completed and person-years observed.

The observation period in each HDSS site varied between 1992 and 2012, with a minimum duration of five years. The Nouna, Burkina Faso, and Agincourt, South Africa, sites had the longest observation time. Overall, there was documentation on 96,255 deaths over 9,487,418 person-years for all ages in the group of sites with at least five years of data. The VAs were completed for 86,039 (89%) of total deaths (76). The 12 HDSS sites included in the analysis for paper II consisted of 10 sites in Africa including Nouna, Burkina Faso; Navrongo and Dodowa, Ghana; Farafenni, the Gambia; Kisumu and Nairobi, Kenya; Karonga, Malawi; Niakhar, Senegal; Agincourt and Africa Centre, South Africa, and two sites in Asia (Matlab and AMK, Bangladesh) (Figure 2).
Since the HDSS sites were not designed to be nationally or regionally representative, aggregated results over sites are not meaningful. Consequently, the basis analysis for comparisons used site-specific, cause-specific mortality fractions (CSMFs) and mortality rates (CSMRs). The INDEPTH 2013 standard population was used to standardise the CSMFs and CSMRs since there are possibilities of inter-site and inter-year variations in the age-sex population structure in each site (77). Cause-specific mortality can be compared between sites by calculating the cause-specific mortality rates with a standardised weight for every combination of site, age group, sex, and year without concern for differences in underlying population structures, hence labelled as age-sex-time standardisation.

**High Income Country – Swedish National Data**

Sweden, which belongs to the category of high-income countries, located in northern Europe, had a total of 9,747,355 inhabitants in 2014, with about half of the total population between the ages of 30 and 70 years (78). Sweden is well-known for highly ranked in numerous comparisons of national performance including quality of life, health, education, equality, economic competitiveness, prosperity and human resource development; has universal health care coverage for its citizens; and as one of the countries in the world that has the oldest national register data. The Swedish government initiated collecting vital data on population size, birth, death and migration through parish clergy in the 18th century. For paper III and IV in this thesis, we utilised data from the Swedish national population-based registers that link individual data on health and its determinants, sourced via the Linnaeus database. The Linnaeus database is a population-based longitudinal database at individual level, established in 2007, financed through a “Linnaeus Grant” and developed through collaboration between interdisciplinary ageing researchers at the Ageing and Living Conditions (ALC) research centre in Umeå University, in collaboration with Statistics Sweden. The Linnaeus database links different sources at the individual level using Swedish personal identity numbers and returns anonymised data to researchers in Umeå. The database consists of several data sources, including register data from Statistics Sweden (demographic and socio-economic data), National Board of Health and Welfare (cause of deaths and hospitalisation data), Västerbotten Intervention Programme (VIP) and Betula (cognitive function and health status inquiries), which are continuously updated. However, the information on hospitalisation and causes of death are available only for people aged 30 years and over since the ALC focus is on ageing. Therefore, paper III analysed deaths that occurred between 30 and 70 years of age. The VIP data used for paper IV consisted of health indicators, life style, socio-economic status and living conditions at individual level, based on decadal follow-up. More detailed information about VIP is given below. Both the VIP and Betula data enrich the extensive Swedish register data by providing substantial sources on health information at individual level, including life style risk factors and cognitive functions.
The Västerbotten Intervention Programme (VIP) is a long-term project proposed for health promotion and cardiovascular disease prevention for the Swedish population living in Västerbotten County in the northern part of Sweden. The VIP was designed using the model for population-based health intervention developed in the North Karelia Project in Finland and adapted for the Swedish context. The VIP was initiated based on previous epidemiological reports on high CVD incidence in Västerbotten County. A pilot intervention programme, designed and implemented by the Västerbotten County Council, was initiated in Norsjö municipality, a smaller municipality in Västerbotten County with the highest CVD mortality. The pilot study intended to carry out systematic life style risk factor screening and provide counselling conducted by skilled primary health care staff, as well as to increase community alertness on CVD (79). Individuals on reaching ages of 40, 50 and 60 were invited to the health promotion programme and given verbal information about their results later. The pilot study was gradually expanded and implemented throughout all municipalities in the Västerbotten County. Since 1991, the County Council has invited all middle-aged population in Västerbotten County to participate in the intervention programme. Full implementations in all municipalities, in which the VIP was integrated into the primary health care programme, were achieved since 1995. The participation rates increased from 57% during 1991-1995 to 67% in 2006. The VIP was designed to be integrated with the local community, including the introduction of a food-labelling system indicating low-fat and high-fibre foods, the promotion of healthy school lunches, and the distribution of health education materials in the community in order to motivate a better healthy lifestyle.

In the invitation letter, the participants were given information to fast overnight before they attended their local health centre for the health examination. They completed health survey questionnaires in primary health care. The health survey questionnaires consisted of demographic and socioeconomic status, self-reported health, and lifestyle risk factors. After the screening programme, individuals with higher risk received further medical advice and counselling by health professionals. A total of 120,929 individuals participated at the ages of 40, 50 and 60 in the VIP from 1991 to 2010. About 29.5% of total participants had two health assessments (when they were invited for a 10-year follow-up after the previous visit), and only 0.9% had three health assessments (80). Many studies have been published using VIP data on different issues related to NCD risk factors (43, 46, 55, 56, 58, 81-95). Detailed analyses will provide insights on the process of implementing and maintaining the intervention, the on-going feasibility of the VIP, its methodology and the benefits from health counselling both from the provider and participant perspectives (79, 96).
2. Study Variables

Outcomes of the Study

The main outcomes of the study were premature mortality from all causes and NCDs, including cardiovascular disease (CVD), cancer, diabetes and chronic respiratory disease. Overall, causes of death had been coded according to the International Classification of Diseases 9th and 10th revisions (ICD-9 and ICD-10) defined by the WHO [4]. The NCD deaths were categorised into four groups based on the ICD-10 codes: cardiovascular disease (I00-I99), cancer (C00-C97), diabetes (E10-E14), and chronic respiratory disease (J30-J98) (32). For the Swedish data analysis (paper III and IV), premature death was defined as deaths occurred between ages of 30 and 69. For mortality data from the INDEPTH Network, premature death refers to those people who died between the ages of 15 and 64, which is in line with the aggregated data provided in the INDEPTH Network database. NCD mortality in the INDEPTH data included neoplasms, metabolic, cardiovascular, respiratory, abdominal, neurological and other NCDs, corresponding to chapters in WHO 2012 VA standard.

Demographic and Socioeconomic Variables

Demographic and socio-economic variables were only used to control for potential confounding and identify effect modification, including age, sex, marital status, education level, employment status, country of birth and area in the Swedish data.

• Age group - we categorised age in decades (30–39, 40–49, 50–59, 60–69) in paper III for calculating unconditional probability using a life table method as specified by the WHO (27). In paper IV, age was categorised into age groups 40, 50 and 60 as the target ages for VIP.

• Marital status was categorised into partnered, single, or widowed/divorced.

• Highest education level was assessed according to the Swedish education system. Completion of 9 years of school was defined as basic education (primary school). Completion of 12 years of school was defined as mid-level education (secondary school). Tertiary education was defined if respondent completed over 12 years of school.

• Employment status was classified into full-time with high, medium, or low income, part-time, or not employed.

• Immigrant status was based on country of birth, which we dichotomised into Swedish-born and foreign-born.

• Living area (only used in paper IV) was categorised into urban area (Umeå) and semi urban (Skellefteå and Lycksele), and rural area (small municipalities and sparsely populated areas).
**Risk Factor Variables**

We derived information on individual NCD risk factors from the first health examination in the VIP study, including current smoking, physical inactivity, obesity, hypertension, raised blood glucose and hypercholesterolaemia.

- Smokers were defined as those who currently smoked tobacco daily or occasionally.
- Physical activity was assessed based on self-reported physical activities related to commuting, recreation and physical exercise. A combination of these activities was used to categorise the respondents into two groups of sedentary or active (46).
- BMI was calculated as weight (in kilograms) divided by the square of the height (in metres). Obesity was defined as BMI ≥ 30kg/m².
- Blood pressure (BP) was measured twice according to clinical guidelines with a mercury sphygmomanometer and the average value of the two measurements was used. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or if individuals used hypertension medication.
- After an overnight fast, all participants not known to have diabetes and with fasting plasma glucose (FPG) <7.0 mmol/L were offered an oral glucose tolerance test (OGTT) performed according to the WHO criteria using a 75 g anhydrous glucose load. Glucose concentrations were measured on capillary plasma samples using Reflotron bench-top analysers until 2004, after which Hemocue bench-top analysers were used (Quest Diagnostics). Raised blood sugar was ascertained from measurements of fasting plasma glucose (≥ 7 mmol/L) or 2-h plasma glucose (≥ 12.2 mmol/L), or self-reported diabetes.
- Serum total cholesterol was analysed from venous blood samples using Reflotron bench-top analysers (Boehringer Mannheim GmbH). The respondents were classified as having hypercholesterolaemia if their total cholesterol levels were ≥6.5 mmol/L, or if they used cholesterol-lowering medication.

**3. Statistical Analyses**

In paper II, we utilised aggregated data from the INDEPTH Network to examine the mortality trends in LMICs from 1992 to 2012. We used the WHO 2012 VA standard and the InterVA-4 model for determining specific causes of death. We focused only in 12 HDSS sites that had observation periods of at least five years, and consisted of 10 sites in Africa (Burkina Faso, two in Ghana, the Gambia, two in Kenya, Malawi, Senegal and two in South Africa) and 2 sites in Asia (Bangladesh). Total observed deaths were 96,255 over 9,487,419 person-years during 1992-2012, of which 89% deaths had complete verbal autopsy interviews. Indeterminate causes accounted for 21.6% of total deaths observed in the dataset. Detailed information on cause of death categories and methodology are available elsewhere (76).
We calculated mortality rates (per 1,000 person-years) for each site, year, sex and age group using age-sex-time standardisation based on the INDEPTH 2013 standard (77). Changes in the age–sex–time standardised mortality—all and cause-specific mortality in all age groups and specifically in adults aged 15-64 years were calculated for each site.

In paper III, we used retrospective cohort data from the Swedish population registers (via the Linnaeus database) covering the national population within the age range 30 to 69 years and records of cause-specific mortality, for the period 1991 to 2006, to construct a dynamic cohort. The mid-year population in Sweden increased from 8,668,066 in 1991 to 9,080,505 in 2006. The proportion of people aged 30 to 69 years increased from 48.4% in 1991 to 51.6% of the 2006 population, as the population aged and the proportion of younger people decreased. To test whether a postulated target of a 25% reduction in the unconditional probability of dying between ages of 30 and 70 from NCD deaths was achieved in Sweden during 1991-2006, mortality was analysed in terms of the unconditional probability of dying from the four NCD groups using a life table method as specified by the WHO (28). Mortality rate ratios were calculated using multivariate Poisson regression analyses to assess which population subgroups were more or less successful in contributing to decreases in premature NCD mortality, using person-years of residence as exposure time and adjusting for age in decades (30–39, 40–49, 50–59, 60–69) and for calendar time in four-year periods (1991–1994, 1995–1998, 1999–2002, 2003–2006).

In paper IV, we used prospective cohort data from the VIP for 1990 to 2006, consisting 62,434 individual observations on risk factor data of blood pressure, total cholesterol, BMI, physical activity, smoking status and blood glucose. A total of 73,800 individual risk factors were accounted for during the period 1990 to 2006, with an average of 1.18 risk factors per VIP participant. At the beginning, we examined the cross-sectional patterns of risk factors over the years of the study. Data from the first three years (1990-1992) were combined and used as the baseline level because the VIP study did not cover all municipalities within Västerbotten County during the first few years from its implementation. Then, we compared the baseline data against risk factor data from subsequent years. We estimated the average annual changes in risk factor according to a regression coefficient from a simple linear regression model, to evaluate if the annual change over the study period was statistically significant.

Then, we estimated the multivariable-adjusted relative risks (RRs) of premature mortality associated with risk factors using Cox proportional hazard regression models for each cohort. However, the analysis revealed homogeneity of RRs related to the risk factors studied between the different cohorts, and observed no time-cohort effect. Therefore, all the annual cohorts were combined to estimate a common RR for each mortality group for the whole period. In further analysis, the attributable contributions of changing risk factors over the study period to various components of premature NCD deaths were calculated using the classical formula for population-attributable risk (PARe) (below) and RRs from the initial model.
\[
    \text{PAR}_e = \frac{P_e (RRe - 1)}{1 + (P_e (RRe - 1))}
\]

where \( P_e \) = proportion of the study population exposed to a particular risk factor in a particular year, and \( RRe \) = relative mortality risk associated with exposure to that same risk factor. The population-attributable risk fractions were calculated for each mortality category, risk factor and year. The relative mortality risks associated with cancer and hypercholesterolaemia, hypertension and obesity were very close to, and not significantly different from, unity, and hence were set to one, giving population-attributable risk fractions of zero. Age-and sex-adjusted mortality rates for each year of the study were calculated using Poisson regression models for various categories of premature mortality as the dependent variable, year and age as independent variables and person-time exposed as the rate multiplier. The same models were used to estimate overall trends by mortality categories. Next, we estimated the effects of changes in premature mortality attributable to changes in risk factor prevalence over time. Then, we decomposed mortality rates using the population attributable risks already calculated to estimate the proportion of various mortality groups attributable to observed risk factors in the same population. Finally, we estimated the associations between various categories of premature mortality and a number of non-communicable risk factors using Poisson regression models, adjusting for sex, age and year and using person-time exposed as the rate multiplier. All analyses were done using STATA software. Because of the very large size of the dataset, hypothesis test leading to \( p \)-values was not particularly helpful. Therefore comparisons were primarily assessed on the basis of 95% confidence intervals (CI).

4. Ethical Approval

Ethical approvals were not required for paper I and II since these studies used publicly available evidence and public domain secondary data. Ethical approval for paper III and IV was obtained from the Regional Ethical Committee at Umeå University, Sweden (Dnr 07-142Ö).
FINDINGS

From paper I, we found a total of 136 articles that satisfied the inclusion criteria, of which 112 articles were performed in single countries and the other 24 articles were conducted in multiple countries. About 37% of 136 articles used historical data before Omran’s theory was postulated in 1970, and the remaining 63% focused more on contemporary societies after 1970. Half of the papers examined both all-cause and cause-specific deaths. Seventy-nine of the articles (58%) reported time trends in outcome indicators, while the remaining 42% reported cross-sectional observations. The majority of the articles (87%) used mortality rates (total, sex specific, age specific or cause specific) and the remainder used absolute numbers or proportions of deaths (9%), DALY (3%), life expectancy and standardised mortality rates (1%).

Many studies have confirmed Omran’s proposition on mortality and its changes, either in absolute numbers of deaths or changes in specific cause of deaths. Many publications confirmed that mortality declined at different speeds among all age groups (23, 97-112) and across specific age groups, including neonates and infants (113-115), children (116, 117), adolescents (118), and adults (119-121). The population based data from INDEPTH support the fact that children and young women were the groups that received the greatest benefits of changes in health and disease patterns in most HDSS sites, which are in line with previous studies (23, 97, 98, 100-102, 107, 108, 116-118, 122-133). Variations in the speed of mortality changes were observed, for example East Asian countries (Japan, Taiwan, Hong Kong, Korea, and China) experienced a significant rapid reduction in mortality during the last half of the 20th century (103, 133-138). The intermediate sub-model refers to LMICs that still face overlapping infectious diseases and NCDs (23, 130, 139-142). The slow sub-model refers to countries that are least prepared to handle the triple burden of disease, typically in African countries that have advanced at a much slower pace than other countries with similar life expectancy levels (143-146). These facts suggest that long-term shifts in patterns of mortality never entirely displace infectious diseases by degenerative and man-made disease and ageing, as Omran described in his theory.

According to Omran’s original theory, all countries experience various stages of ET over time. We mapped some countries studied from the systematic review and INDEPTH data (in italics) to different sub-models, which account for differences in timing and pace of ET in LMICs (Table 1). Industrialised countries generally started ET earlier but proceeded slowly. Western European countries (Sweden, United Kingdom, and France) faced a shift from stage 2 to stage 3 of ET mostly in the 19th century and then took a further half-century from stage 3 to stage 4 (108, 147-149). Cuba, USA, and Australia entered stage 2 later than European countries and then reached stage 3 almost at the same time (100, 101, 119, 125, 150), while the Netherlands entered stage 1 later than USA and Australia (151). Hungary experienced a rapid shift from stage 2 to stage 3 at the end of the 20th century, after the rapid political changes, and is now in stage 4 of ET with declining cardiovascular mortality and increasing life expectancy (152). During 1978-1996, Canada experienced a significant decline in CVD mortality.
(characteristic of stage 4) (153). Heterogeneity in stages of ET were observed in the former Soviet Union such that the male population in the northern part experienced higher mortality due to chronic diseases, such as cardiovascular diseases, injuries, and lung cancer than in the southern part (154, 155). Our study (paper II) showed that most African countries faced stage 1 of epidemiological transition with predominant communicable disease mortality over time, except in the Navrongo, Ghana site and the South African sites (Agincourt and Africa Centre).

The applicability of the epidemiological transition model has been questioned in the last few decades. We found the sequential staged process proposed by the ET model did not reflect epidemiological changes in some countries. Eastern and central European countries (176), former Soviet republics (177, 178), Mexico (23) and some African countries (97, 143, 146, 179, 180) were examples of countries that have encountered serious obstacles preventing them from completing certain stages of the transition. Even reversal of mortality trend was observed in Nauru (181-183), USA (125), Russia (136), Tanzania (184) and Thailand (171). Mortality trends in the Tsimane communities in Bolivia showed decreased instances of deaths due to infectious diseases but increased instances of accidents and violence, particularly in the middle and late adulthood, which demonstrates a different pattern from the classical ET theory (185). A substantial different shift in mortality trend was observed among adults in France during 1988-1999, where declining infectious disease mortality was not followed by increasing NCD mortality but instead by greater HIV infection, injury and poisoning (147). In Nauru, previously high mortality from infectious diseases transitioned very rapidly into extremely high mortality from diabetes, circulatory disorders, and accidents over a short period, thus denying appreciable increases in life expectancy (181). Meanwhile a cluster analysis conducted in the Netherlands found that mortality decline in infectious diseases and the rise in non-infectious diseases had different time trends, in contrast with the classical interpretation of the ET that assumes uniform changes (151). Kovacs and his colleagues observed that mortality patterns in Hungary during 1971-2007 differed from what might be expected in the fourth stage of ET in that female death rates increased due to ischaemic heart disease, while deaths related to external injuries declined and no evidence of emergent or re-emergent diseases was found (186). In Canada, the decline in mortality related to cardiovascular disease was mostly concentrated in advanced ages and the decline did not occur at the same pace for men and women, so the shifting pattern of causes of death did not entirely fit the theory (162, 187). High mortality burdens from external causes, such as violence, in El Salvador did not follow cause of death patterns elsewhere which were predominated by infectious diseases at early stages of transition (188).
Table 1: Timeline of selected countries reported to be at various stages of epidemiological transition. Table is modified from Global Health Action. 2014 (27).

<table>
<thead>
<tr>
<th>Year Period</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1870-1874</td>
<td>United Kingdom, Sweden, Finland, Iceland (156, 157), USA (125), Germany (158)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1875-1879</td>
<td>the Netherlands (151)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1900-1904</td>
<td>Spain (107, 113, 123)</td>
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<td></td>
<td></td>
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<tr>
<td>1905-1909</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>1910-1914</td>
<td>United Kingdom, Sweden, Finland, Iceland (108, 156, 157), the Netherlands (151)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1915-1919</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1920-1924</td>
<td>Mexico (23)</td>
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<tr>
<td>1925-1929</td>
<td></td>
<td></td>
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<tr>
<td>1930-1934</td>
<td>Germany (158)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1935-1939</td>
<td>Japan (103)</td>
<td></td>
<td></td>
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<tr>
<td>1940-1944</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1945-1949</td>
<td>Costa Rica (106)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1950-1954</td>
<td>Hong Kong (160), Trinidad and Tobago (104, 127)</td>
<td>Japan (103, 133), Ghana (97), Canada (161, 162)</td>
<td>United Kingdom (108, 156, 157), the Netherlands (151), Sweden, Iceland (156, 157),</td>
<td></td>
</tr>
<tr>
<td>1955-1959</td>
<td>Peru (163)</td>
<td>China (133)</td>
<td></td>
<td></td>
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<tr>
<td>1960-1964</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1965-1969</td>
<td>Hong Kong, Singapore (160)</td>
<td>Spain (107, 113, 123), Costa Rica (106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1970-1974</td>
<td>Trinidad and Tobago (104, 127), Korea (129)</td>
<td>Japan (133), Mauritius (99), Canada (161)</td>
<td>Netherland (151)</td>
<td></td>
</tr>
<tr>
<td>1975-1979</td>
<td></td>
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<tr>
<td>1980-1984</td>
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<tr>
<td>1985-1989</td>
<td>Mexico (164, 165)</td>
<td>Hong Kong, Malaysia (166)</td>
<td>Costa Rica (106), Canada (162), Spain (159), Japan (133), France (147), Australia (119, 168), Trinidad and Tobago (104)</td>
<td></td>
</tr>
<tr>
<td>1990-1994</td>
<td>Peru (163)</td>
<td>Seychelles (167), Ghana (97), Cuba (150)</td>
<td>Japan (133), France (147), Australia (119, 168), Trinidad and Tobago (104)</td>
<td></td>
</tr>
<tr>
<td>1995-1999</td>
<td>Burkina Faso (Nouna), Gambia (Farafenni), South Africa (Agincourt)</td>
<td>Mexico (169)</td>
<td>Korea (169)</td>
<td>China (133)</td>
</tr>
<tr>
<td>2000-2004</td>
<td>Burkina Faso (Nouna), Gambia (Farafenni), Kenya (Kisumu), Malawi (Karonga), South Africa (Africa Centre)</td>
<td>Ghana (Navrongo)</td>
<td>India (102, 121), Thailand (170, 171), Bangladesh (AMK and Matlab)</td>
<td>Mexico (142), Peru (172), Hungary (152), Brazil (120, 173, 174)</td>
</tr>
<tr>
<td>2005-2009</td>
<td>Burkina Faso (Nouna), Ghana (Dodowa), Kenya (Kisumu, Nairobi), South Africa (Africa Centre)</td>
<td>Ghana (Navrongo)</td>
<td>Bangladesh (AMK and Matlab)</td>
<td>Vietnam (141), Mexico (175)</td>
</tr>
<tr>
<td>2010-2012</td>
<td>Kenya (Nairobi)</td>
<td>Malawi (Karonga), South Africa (Africa Centre)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
The conceptualised protracted polarised transition model was observed in Ghana (97), South Africa (180), Peru (163, 172, 189) and Mexico (23), indicating a double burden of persistent communicable diseases and NCDs, along with injuries and emerging/re-emerging infections (tuberculosis, malaria, HIV/AIDS). In case of Mexico, they faced overlapping burdens of infectious disease and increasing trend of NCDs among the younger age groups during 1922-1955, due to poverty and inability to afford healthcare (23). Similar patterns of protracted transition observed from the INDEPTH data. We found that Nouna (Burkina Faso) and Navrongo (Ghana) experienced an overlap mortality burden from communicable disease and NCD with persistent mortality related to malaria. Mortality trends in Agincourt HDSS (South Africa) indicated a quadruple burden of mortality due to communicable diseases, NCDs, injury and HIV/AIDS during 1992-2011, with an increase trend in deaths before the age of 64 years.

In the late 20th century, new infectious diseases such as HIV/ AIDS and Avian influenza showed remarkable abilities to spread as global epidemics due to population growth, unplanned urbanisation, anti-microbial resistance, poverty, and lifestyle changes in communities. AIDS still persists as a major global health concern although medical technology and treatment has progressed in preventing new HIV infections and AIDS-related deaths. Although HIV/AIDS epidemic reports mostly focus on national trends, there are often large variations in HIV prevalence and epidemiological patterns within countries. The epidemic of HIV/AIDS appears to have stabilised in most countries, with sub-Saharan Africa remaining the most heavily affected region, accounting for 71% of newly infected HIV cases in 2010. The AIDS epidemic triggered a decrease, and in some cases a sharp drop, in the life expectancy levels in many African countries, which is bound to influence any interpretation of their progress in ET terms. Downward trends in mortality have been reversed in some areas as a consequence of the HIV/AIDS pandemic. The HIV/AIDS epidemic also observed in Thailand since 1990 caused a decrease in life expectancy by 4 years during 1990-2000 (171).

According to the ET model, children and women were groups that experience the most obvious changes in health and disease patterns. However, previous studies from Bolivia (185), Nauru (181), Thailand (171) (154), and South Africa (97, 143, 146, 179, 180) found a stable or increasing mortality rate among infants, children and women. Declining mortality rates were not observed among children and young women in some INDEPTH HDSS e.g. Agincourt, Farafenni and Nairobi HDSS, which were mostly due to increase of HIV/AIDS in Agincourt, acute respiratory infections in Nairobi and endemic malaria in the Gambia. All these examples support existing criticisms that ET theory fails to describe the transition in some countries due to complexities of socio-economic, historical, political, and cultural factors that caused deviations from certain stages of the transition. Therefore, Omran’s ET theory and its later developments cannot predict changes in mortality and cause-of-death patterns across all countries and time periods, as noted previously in some earlier reviews by Caselli et al. (17) and Gaylin and Kates (16).
In paper II, we documented a total of 96,255 deaths from 12 selected HDSS sites, over a total of 9,487,418 person-years. Of all deaths, 28.4% occurred in children aged 0-14 years; 43.3% in adults aged 15-64 years and 28.3% in older people aged 65+. The highest all-cause mortality rates after age-sex-time standardisation were observed in the Kisumu, Kenya and Africa Centre, South Africa sites (18.5 and 15.3 per 1,000 person-years, respectively). Mortality rate among children declined over time in most INDEPTH sites, excluding Agincourt, Farafenni and Nairobi (data not shown). Table 2 shows age-sex-time standardised mortality rates per 1,000 person-years and annual changes for cause specific deaths in all age groups and for adults aged 15-64 years in selected INDEPTH HDSS sites during the period 1992 to 2012. The trends in mortality rates in all age groups within INDEPTH sites clearly showed declines over time in most sites, as shown in Figure 3. The age-sex-time standardised mortality rate declines appeared approximately linear over the time period, except in South African sites. In the Agincourt, South Africa, site, mortality rate showed different pattern compared to other sites, which the rate increased from 1992 and reached a peak in 2007 due to the HIV epidemic and later decreased again. However, the decreasing mortality rates particularly for HIV and pulmonary TB were not followed by other causes of death such as NCDs and external causes. Mortality rates in Bangladeshi sites (Matlab and AMK) were relatively stable during the period 2003-2010. For most INDEPTH sites, communicable diseases still accounted for the largest mortality rates in all age groups over time. Communicable mortality rates were substantially higher in Kisumu, Kenya site (10.9 per 1,000 person-years) and Africa Centre, South Africa site (8.25 per 1,000 person-years), in which malaria (in Kenya) and HIV/AIDS (in both sites) contributed major components of childhood mortality. NCD mortality rates were higher than other major cause groups in Matlab and AMK, Bangladesh and Navrongo, Ghana. Injuries and maternal causes accounted for small contributions of total deaths.

After age-sex-time standardisation, a total of 48,589 premature deaths were documented in the 15-64 year age group during the period 1992 to 2012, consisting of deaths related to communicable diseases (48%), NCD (23.8%), maternal (1.3%) and injury (7.4%). The premature adult deaths accounted for 43.3% of total deaths observed in the INDEPTH data, with the highest proportion of premature death in South Africa (Africa centre) and Kenya (Nairobi). Upward trends in the burden of premature deaths were observed in some INDEPTH sites (Dodowa and Navrongo, Ghana sites and Agincourt and Africa Centre, South Africa, sites), reflecting a considerable burden of chronic disease in the productive age group. Premature deaths due to communicable disease still dominated in most HDSS sites, except in the Navrongo, Ghana site and Bangladesh sites.
Table 2: Age-sex-time standardised mortality rates per 1,000 person-years and annual changes for specific causes of deaths in all age groups and adults aged 15-64 years in selected INDEPTH HDSS sites during the period 1992 to 2012.

<table>
<thead>
<tr>
<th>Site</th>
<th>Period</th>
<th>All ages</th>
<th>15-64 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standa</td>
<td>Annual</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rdised</td>
<td>change (%)</td>
</tr>
<tr>
<td>Bangladesh (Matlab)</td>
<td>2003-2010</td>
<td>10,812</td>
<td>-2.5</td>
</tr>
<tr>
<td>Bangladesh (AMK)</td>
<td>2004-2010</td>
<td>3,116</td>
<td>-3.0</td>
</tr>
<tr>
<td>Burkina Faso (Nouna)</td>
<td>1998-2009</td>
<td>6,471</td>
<td>-7.4</td>
</tr>
<tr>
<td>Ghana (Navrongo)</td>
<td>2004-2011</td>
<td>11,429</td>
<td>-7.1</td>
</tr>
<tr>
<td>Ghana (Dodowa)</td>
<td>2006-2010</td>
<td>4,033</td>
<td>-9.0</td>
</tr>
<tr>
<td>Gambia (Farafenni)</td>
<td>1998-2007</td>
<td>3,348</td>
<td>-6.0</td>
</tr>
<tr>
<td>Kenya (Kisumu)</td>
<td>2003-2010</td>
<td>20,965</td>
<td>-2.6</td>
</tr>
<tr>
<td>Kenya (Nairobi)</td>
<td>2003-2012</td>
<td>6,145</td>
<td>-5.3</td>
</tr>
<tr>
<td>Malawi (Karonga)</td>
<td>2003-2010</td>
<td>2,422</td>
<td>-7.1</td>
</tr>
<tr>
<td>Senegal (Niakhar)</td>
<td>2005-2010</td>
<td>1,830</td>
<td>-12.0</td>
</tr>
<tr>
<td>South Africa (Agincourt)</td>
<td>1992-2011</td>
<td>13,153</td>
<td>3.4</td>
</tr>
<tr>
<td>South Africa (Africa Centre)</td>
<td>2000-2011</td>
<td>12,459</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

Note: Comm. = Communicable
Overall, the leading communicable causes of premature death were pulmonary tuberculosis and acute respiratory infectious disease in most African HDSSs, except in Kenya and South Africa where HIV/AIDS and pulmonary tuberculosis were the most common communicable causes of death. Trends in premature mortality rates per 1,000 person-years across INDEPTH HDSS sites for major causes of death are shown in Figure 4. Overall, in most African sites, mortality rates declined except in the Agincourt, South Africa, site where mortality rate increased from 5 per 1,000 person-years in 1992 and reached a peak in 2008 (12.7 per 1,000 person-years), then decreased slightly afterwards. The upward trend of mortality rates observed in Agincourt, South Africa site during 1992-2011 was due to epidemic HIV/AIDS and pulmonary tuberculosis.
In case of the Kisumu, Kenya, site, mortality rates declined until 2007, but then it increased again within a year due to endemic malaria and HIV/AIDS. Meanwhile premature mortality rates particularly from NCDs were relatively stable in Bangladesh sites (Matlab and AMK) during period 2003-2010. The breakdown of overall premature age-sex-time standardised mortality rates by cause category and site, as shown in Figure 5, showed that neoplasms and CVD were the main cause of death within the overall burden of premature NCD deaths. The corresponding communicable disease causes were HIV/AIDS and pulmonary tuberculosis. Road traffic accidents and assault accounted for the largest proportion of premature deaths among external cause. Although external cause deaths accounted for a very small proportion of total deaths among adults aged 15-64 year, age-sex-time standardised mortality rates increased in some sites e.g. Nairobi, Kenya site and Karonga, Malawi.
We found various trends in sub-categories of NCD mortality in adults aged 15-64 years. A steady decline was observed in Nouna (Burkina Faso), Farafenni (Gambia), Karonga (Malawi). In contrast a continuous increase was observed in Agincourt (South Africa) and Matlab (Bangladesh), which were largely driven by increases in neoplasms and cardiovascular.

In paper III, we documented a total of 292,320 deaths that occurred in the 30–69 year age group during the period 1991 to 2006, against 70,768,848 individually registered person-years for the same age range, corresponding to a crude mortality rate of 4.13 per 1,000 person-years. Out of the total deaths, 215,185 (73.6%) met the WHO definition of premature NCD deaths, comprising cardiovascular (41.8%), cancer (51.7%), diabetes (2.6%), and chronic respiratory diseases (3.9%).
Figure 6: Overall unconditional probabilities of dying between the ages of 30 and 70 in Sweden from 1991 to 2006, showing non-communicable disease mortality split between cardiovascular, cancer, diabetes and chronic respiratory causes, and all other causes of death. Figure is reproduced from BMC Medicine, 2015 (190).

Figure 7: Adjusted mortality rate ratios and 95% confidence intervals for premature non-communicable disease mortality for the 30 to 69 year age group in Sweden by time period and background factors, using Poisson regression models for each time period. Figure is reproduced from BMC Medicine, 2015 (190).
The unconditional probability of death between the ages of 30 and 70 years from all causes fell by 26.6% in Sweden during 1991-2006. The corresponding decline for premature death from NCD was a decrease of 30.0% for the same period, of which 54.2% of the overall reduction occurred in the first half of the period. Therefore, the postulated target of a 25% reduction was clearly met, with the largest reduction being from CVD mortality changes (48.3%), as shown in Figure 6. However, cancer rates, as the largest of the four components of NCD mortality, declined more modestly (15.5%). Mortality attributed to diabetes accounted for a small proportion of overall mortality and did not contribute appreciably to overall reductions, having reduced by only 1.5%.

Chronic respiratory disease was also a minor contributor to overall mortality at national level, with a reduction of 19.7% from 1991 to 2006. Using a Poisson regression model, we calculated the adjusted mortality rate ratio with 95% confidence interval for causes of death and background factors for the 30 to 69 year age group in Sweden during 1991 to 2006, for each death category (Table 3) and for each period of time (Figure 7). It is clear that many of the background factors examined in paper III were inter-related, particularly age in relation to marital, educational, and employment status. Age group, and to a lesser extent education, became increasingly strong determinants of NCD mortality as time passed. Employment, sex, marital status, and migration status became less strongly associated with NCD mortality as time passed. Excess mortality among males persisted over the four time periods.
Table 3: Adjusted multivariate Poisson regression models of mortality rate ratios for causes of death and background factors for the 30 to 69 year age group in the Swedish population during 1991 to 2006. Table is reproduced from BMC Medicine, 2015 (190).

<table>
<thead>
<tr>
<th></th>
<th>All causes</th>
<th>Non-communicable disease causes</th>
<th>Other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>Cancer</td>
<td>Diabetes</td>
</tr>
<tr>
<td><strong>Sex</strong> (reference: Female)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.93 (1.91–1.94)</td>
<td>3.18 (3.14–3.23)</td>
<td>1.14 (1.12–1.15)</td>
</tr>
<tr>
<td><strong>Age group</strong> (reference: 30–39 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49 years</td>
<td>2.99 (2.93–3.05)</td>
<td>5.39 (5.11–5.69)</td>
<td>4.02 (3.86–4.19)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>7.88 (7.74–8.03)</td>
<td>19.3 (18.3–20.3)</td>
<td>12.8 (12.3–13.3)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>17.0 (16.7–17.3)</td>
<td>52.5 (49.9–55.3)</td>
<td>29.9 (28.8–31.1)</td>
</tr>
<tr>
<td>1999–2002</td>
<td>1.06 (1.05–1.07)</td>
<td>1.18 (1.15–1.20)</td>
<td>1.01 (1.00–1.03)</td>
</tr>
<tr>
<td>1995–1998</td>
<td>1.07 (1.06–1.08)</td>
<td>1.23 (1.21–1.26)</td>
<td>1.02 (1.01–1.04)</td>
</tr>
<tr>
<td>1991–1994</td>
<td>1.01 (1.00–1.02)</td>
<td>1.17 (1.15–1.20)</td>
<td>0.99 (0.97–1.00)</td>
</tr>
<tr>
<td><strong>Marital status</strong> (reference: partnered)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>1.58 (1.57–1.60)</td>
<td>1.68 (1.65–1.70)</td>
<td>1.13 (1.11–1.14)</td>
</tr>
<tr>
<td>Widowed/divorced</td>
<td>1.68 (1.67–1.70)</td>
<td>1.71 (1.68–1.74)</td>
<td>1.28 (1.26–1.30)</td>
</tr>
<tr>
<td><strong>Education level</strong> (reference: tertiary)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper secondary</td>
<td>1.23 (1.21–1.24)</td>
<td>1.37 (1.34–1.40)</td>
<td>1.12 (1.10–1.14)</td>
</tr>
<tr>
<td>Lower secondary</td>
<td>1.37 (1.35–1.39)</td>
<td>1.50 (1.45–1.55)</td>
<td>1.14 (1.12–1.17)</td>
</tr>
<tr>
<td>Primary</td>
<td>1.40 (1.38–1.42)</td>
<td>1.68 (1.64–1.72)</td>
<td>1.23 (1.20–1.25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.31 (1.27–1.34)</td>
<td>1.43 (1.36–1.50)</td>
<td>1.21 (1.15–1.26)</td>
</tr>
<tr>
<td><strong>Employment status</strong> (reference: full-time – high income)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time – mid income</td>
<td>1.24 (1.22–1.26)</td>
<td>1.26 (1.23–1.30)</td>
<td>1.16 (1.13–1.19)</td>
</tr>
<tr>
<td>Full-time – low income</td>
<td>1.80 (1.77–1.83)</td>
<td>1.86 (1.81–1.92)</td>
<td>1.42 (1.38–1.46)</td>
</tr>
<tr>
<td>Part-time employment</td>
<td>1.73 (1.69–1.78)</td>
<td>1.70 (1.62–1.78)</td>
<td>1.30 (1.25–1.35)</td>
</tr>
<tr>
<td>Not employed</td>
<td>3.31 (3.26–3.37)</td>
<td>3.88 (3.76–4.00)</td>
<td>1.83 (1.78–1.88)</td>
</tr>
<tr>
<td><strong>Migration status</strong> (reference: in-migrant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swedish-born</td>
<td>1.42 (1.40–1.44)</td>
<td>1.49 (1.45–1.52)</td>
<td>1.39 (1.36–1.42)</td>
</tr>
</tbody>
</table>
In paper IV, we assessed reduction in premature deaths attributable to the risk factor changes. A total of 1,799 deaths occurred among VIP participants before they reached age of 70 years, consisting 553,921 person-years of observation, of which 1,470 (82%) were due to NCDs, including 565 cardiovascular deaths, 854 cancer deaths, 11 diabetes deaths and 40 deaths due to chronic respiratory disease. Figure 8 shows the changes in NCD risk factor prevalences from baseline to 2006. Downward trends of smoking, hypercholesterolaemia and hypertension were observed, with overall annual decreases of 0.64%, 0.37% and 1.15%, respectively. In contrast, prevalences of physical inactivity, obesity and raised blood pressure increased by 0.02%, 0.58% and 0.12% annually. The cumulative decreases in the prevalence of smoking, hypertension and hypercholesterolaemia among VIP participants during 1990-2006 were 10.6%, 7.3% and 13.4%, respectively. In contrast, the cumulative increases in the prevalence of obesity, physical inactivity and raised blood glucose were 7.8%, 1.1% and 2.1%, respectively. Decreases in smoking prevalence were mostly observed in the younger age group. While increases in obesity occurred in all age groups, physical inactivity and raised blood glucose increased among older people.

Figure 8: Percentage changes in non-communicable diseases risk factor prevalence (hypertension, hypercholesterolaemia, obesity, physical inactivity, smoking and raised blood glucose) from baseline (1990-1992) to 2006, measured among 62,434 individual participants aged 40, 50 and 60 years in the Västerbotten Intervention Programme.

Age-adjusted premature mortality rates declined for non-communicable mortality, cardiovascular mortality and cancer mortality over the period 1990 to 2006, with an annual reduction of 3.1% for NCDs, 4.1% for CVD, and 2.8% for cancer, as shown in Figure 9. Overall reduction in attribution of the risk factor to premature non-communicable disease mortality, as shown in Table 4, was 40.1% in baseline and 32.8% in 2006. While attributable contributions of the risk factor to cause of premature NCD mortality were higher for premature cardiovascular mortality (from 76.2% to 67.7%) than premature cancer mortality (from 19.3% to 15.8%).
Figure 9: Age-adjusted premature mortality rate trends for non-communicable disease mortality, cardiovascular mortality and cancer mortality over the period 1990 to 2006, based on 1,470 deaths over 553,921 person-years of observations among individual participants aged 40, 50 and 60 years in the Västerbotten Intervention Programme.

Table 4: Average risk factor prevalence and attributable contributions of risk factors to cause of premature death categories, at baseline (1990-1992) and 2006, among 62,434 individual participants aged 40, 50 and 60 years in the Västerbotten Intervention Programme.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Average prevalence (%)</th>
<th>Attribution of risk factors to premature death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Age 40</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>22.5</td>
<td>11.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33.7</td>
<td>14.7</td>
</tr>
<tr>
<td>Obesity</td>
<td>14.8</td>
<td>12.7</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>18.0</td>
<td>18.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>22.4</td>
<td>21.5</td>
</tr>
<tr>
<td>Raised blood glucose</td>
<td>4.8</td>
<td>1.7</td>
</tr>
</tbody>
</table>
The compound effects for individuals having multiple non-communicable disease risk factors on premature mortality from various causes of death groups, adjusted for sex, age and year, as shown in Table 5, showed that the premature mortality rate ratios (MRR) for various causes of death were higher among people with multiple risk factors, which was seen particularly in relation to cardiovascular mortality.

Table 5: The compound effect of total number of individual risk factors to the age-and sex-adjusted mortality rate from various causes of deaths, expressed as mortality rate ratios, based on 1,470 deaths over 553,921 person-years of observation among individual participants aged 40, 50 and 60 years in the Västerbotten Intervention Programme (zero risk factors as reference group).

<table>
<thead>
<tr>
<th>Total risk factors</th>
<th>All cause</th>
<th>NCD</th>
<th>CVD</th>
<th>Cancer</th>
<th>Non-NCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.32 (1.14-1.54)</td>
<td>1.39 (1.17-1.65)</td>
<td>2.42 (1.67-3.51)</td>
<td>1.15 (0.95-1.40)</td>
<td>1.08 (0.78-1.51)</td>
</tr>
<tr>
<td>1</td>
<td>1.86 (1.60-2.16)</td>
<td>1.87 (1.58-2.22)</td>
<td>4.35 (3.03-6.26)</td>
<td>1.30 (1.06-1.60)</td>
<td>1.83 (1.32-2.53)</td>
</tr>
<tr>
<td>2</td>
<td>2.55 (2.16-3.02)</td>
<td>2.70 (2.24-3.25)</td>
<td>7.52 (5.17-10.9)</td>
<td>1.53 (1.20-1.96)</td>
<td>2.00 (1.36-2.95)</td>
</tr>
<tr>
<td>3</td>
<td>3.03 (2.41-3.81)</td>
<td>3.17 (2.46-4.08)</td>
<td>9.33 (6.03-14.5)</td>
<td>1.62 (1.12-2.34)</td>
<td>2.51 (1.45-4.33)</td>
</tr>
<tr>
<td>4 or more</td>
<td>6.20 (4.29-8.97)</td>
<td>6.04 (3.98-9.16)</td>
<td>20.7 (11.3-38.0)</td>
<td>2.70 (1.38-5.28)</td>
<td>6.99 (3.18-15.4)</td>
</tr>
</tbody>
</table>

The various NCD risk factors attributable to fractions of age-and sex-adjusted mortality rates over time for premature NCD mortality, premature CVD mortality and premature cancer mortality are shown in Figure 10. Since there were insufficient numbers of deaths certified as diabetes or chronic respiratory disease to analyse these mortality categories in terms of the same annual progression, we only measured the major cause of premature NCD deaths (CVD and cancer). Grey areas represent the other component of mortality not attributable to any of the NCD risk factors, while coloured areas represent the premature mortality attributable to the observed risk factors. The observed NCD risk factors accounted for a substantially larger proportion of cardiovascular deaths than cancer deaths, with various risk factor patterns. Figure 11 shows that hypertension and smoking were the two risk factors attributed with the largest components of premature mortality, while smoking was attributed to both cardiovascular and cancer premature mortality. The attributable contributions of obesity and physical inactivity to NCDs and cardiovascular mortality increased slightly, as did the contribution of physical inactivity to cancer, but all other attributable contributions decreased.
Figure 10: Attributable age-and sex adjusted premature mortality from non-communicable disease, cardiovascular disease and cancer to the observed risk factors from baseline to 2006, based on 1,470 deaths over 553,921 person-years of observations among individual participants aged 40, 50 and 60 years in the Västerbotten Intervention Programme.
Summary of the Main Findings

1. Countries experienced different stages of epidemiological transition in terms of timing, pace and underlying mechanisms. Elements of epidemiological transition have been described in many countries, but observed transitions have not always followed the pathways described in Omran’s original theory. The emphasis of epidemiological transition research has changed over the past four decades, with an increasing tendency to study wide-ranging aspects of the determinants of mortality, including risk factors (lifestyle changes), socio-economic determinants and macro factors such as climate change.

2. Different stages of epidemiological transition were observed in African and Asian sites in the last decade, with some expected transition processes and some extraordinary transition processes. Upward trends in the burden of premature death were observed in some INDEPTH sites (South Africa and Ghana) although communicable disease was still the leading category of premature mortality in African sites.

3. Sweden is at relatively late stage of epidemiological transition, and has already exceeded the 25% premature NCD mortality reduction target during an earlier 15-year period, which should be encouraging news for countries currently implementing premature NCD mortality reduction programmes.

4. Downward trends in risk factors have reduced premature NCD mortality in middle-aged people in northern Sweden from 1990 to 2006, but some benefits were offset by other risks increasing. Smoking, hypertension and hypercholesterolaemia were the major attributable risk factors contributing to premature NCD deaths.
DISCUSSION

1. Transition in a Global Context

Epidemiological transition theory, a framework that postulates a descriptive historical experience of the secular decline in mortality and fertility and related changes in the pattern of diseases and causes of death, has mostly been used in public health because it offers an explanation for changing cause of death patterns in accordance with the various stages of transition. Through paper I, we synthesise the substantial variation in empirical evidence that both support and contradict the original proposition of Omran, and highlight the important role of social determinants of health in contributing to the deviation to these propositions. We found some evidences to illustrate the changing pattern of causes of death, as shown in Table 1, which is in line with what Omran proposed in the stages of epidemiological transition over time. But we also noticed some newer evidences that deviated from the original concept (proposition two), such as in Nauru where high mortality from infectious diseases gave way to quite high mortality from diabetes, circulatory disorders and accidents over a short period without any appreciable increases in life expectancy (183); an overlapping burden of disease and an increasing trend of non-communicable diseases at younger ages in Mexico during 1922-1955 due to poverty and unaffordability of healthcare (23); and decreasing mortality trends for infectious disease that did not shift to an increase in NCD mortality despite increased instances of accidents and violence in the middle and late adulthood in Bolivia (185).

The third proposition is fulfilled, that children and women are the groups that experience the most obvious changes in health and disease patterns in most published articles. However, persisting or increasing mortality rates in infants, children and women were observed in Bolivia (185), Nauru (183), Thailand (171), and South Africa (97, 143, 146, 179, 180). All of these examples support the existing criticism that the ET theory fails to describe the transition in some countries due to the complexity of socio-economic factors, history, politics, and culture that causes deviations at certain stages of transition. The development of epidemiological transition in western countries was seen as a result of economic growth and industrialisation, as well as better sanitation and vaccination coverage. Meanwhile, the development of ET in contemporary society in general is driven by medical innovation, economic growth and urbanisation. Based on our findings in paper I, we show that most of the empirical evidence published in the last four decades support the transition framework of demographic, epidemiological and health, although those published evidences are scanty in determining a comprehensive representation of pass and current situation at regional, sub-national, national and global level.

We also observed that there were shifts in the emphasis within epidemiological transition researches over the past four decades, from focusing on mortality trend and associated causes of death to wide-ranging aspects of the determinants of mortality, comprising risk factors and its changes, socio-economics determinants.
and other factors such as climate change. The demographic and socio-economic determinants including factors such as sex, income level, education level, marital status, ethnicity, and regional differences, as well as wider structural and environmental factors, appear to have had great influence on the transition process, even leading to some unequal health conditions as shown in some countries (111, 131, 191-194). Demographic and socio-economic transitions are well known to be considerably associated with health improvement; however, the consequences of socio-economic development and globalisation have been unfavourable in some countries. For example in Russia, economic reform did not produce any tangible economic and social benefit and even led to stagnant or deteriorating health status (136). However, little research has concentrated on linking progress in LMICs in the last four decades with the original ET theory due to the lack of comprehensive data on morbidity and mortality.

2. Transitions in Low- and Middle-Income Countries

The INDEPTH Network, as an international network of health research, has conducted routine vital event surveillance in a number of Health and Demographic Surveillance System sites in LMICs over time, which significantly bridges the gap in reliable and available population-based data on health in LMICs. The availability of long-term demographic and health surveillance data within the INDEPTH Network (paper II) allowed us to gain understandings of trends in population-based mortality rates, overall and by year, cause, age group, and sex over the period 1992-2012, where suitable age-sex-time standardisation of rates allowed systematic comparisons between sites. Findings from INDEPTH data showed some empirical evidences in relation to the current stage of epidemiological transition faced by INDEPTH sites, either the observed mortality pattern over time support or deviate from the classical ET theory. Overall mortality rates have decreased in most sites, led to increased life expectancy, excluding South Africa and Kenya where increases in HIV/AIDS and pulmonary TB disrupted classical transition. Communicable disease mortality remained as the leading cause of death in most African sites, particularly between the ages of 15 and 64 years. Consistent findings on trends in mortality rates are in line with previous studies (76, 144, 195-198). Increasing communicable diseases in South African and Kenyan sites caused a reversal in the trends of decreasing mortality rates, especially for adults, causing a significant decrease in life expectancy (197, 198). A downward trend in mortality rates from HIV/AIDS and pulmonary TB observed since 2008 in Agincourt, South Africa site and 2009 in Kenya, due to the availability of anti-retroviral therapy at public hospital and health centres, has been found in previous studies (76, 199). We found that population-based rates of NCD mortality were relatively constant across the sites compared with the variations in overall mortality, which was largely determined by the large scale of communicable disease.
The evidence from INDEPTH data clearly shows that some countries have not entered any evidence-based shift from one epidemiological stage to another and have not seen the demographic changes and health improvements which would be predicted from demographic, epidemiological, and health transition frameworks or from the global trends when they are compared to other LMICs. A protracted epidemiological transition model, actually a model of quadruple burden of mortality in terms of the persisting communicable disease mortality, increasing burden of avoidable NCDs mortality, injury mortality and re-emerging HIV/AIDS and pulmonary tuberculosis particularly in adults group (15-64 years), was observed in Ghana (Navrongo) and South Africa over the last decade. The emerging pattern of disease in the African sites showed overlapping mortality from communicable and NCDs, in contrast to the expected shift between communicable and NCDs in classical ET theory. The mortality rates from emerging or re-emerging infectious diseases such as TB, malaria, and HIV/AIDS have been persisting or even rising, coinciding with increasing NCD mortality namely cancer, CVD, chronic respiratory and diabetes, which were in line with previous studies (76, 144, 180, 195, 196, 199, 200). According the Global Burden of Disease Study 2010, the impact of HIV/AIDS is projected to at least double the burden of premature mortality (201). Mortality trends observed in INDEPTH countries are sharply different from the historical experiences in developed countries that were described by Omran (5), and deviated from the predicted patterns of epidemiological and health transition frameworks. Our findings in relation to the pattern of epidemiological transition in settings with diverse backgrounds of socio-economic and health information systems in Africa and Asia clearly constitute grounds for urgent public health action. In brief, this thesis revealed that LMIC's epidemiological and health transitions are significantly different from those experienced by the western countries.

Some findings from the INDEPTH data support a deviation from ET theory stages. For example, while most sites achieved improvements in child mortality, increase in childhood mortality rates occurred in Agincourt, Farafenni and Nairobi HDSSs in which were mostly due to increase of HIV/AIDS in Agincourt, acute respiratory infections in Nairobi and endemic malaria in Farafenni. Despite remarkable improvements in childhood mortality, the INDEPTH sites are experiencing inevitably increasing burdens of NCDs among older people (65+) as well as increasing burdens of premature deaths (adult ages of 15 to 64), although the proportion of older people are rather low at present time but expected to increase rapidly in future. A persistent or upward trend in NCD mortality is observed in Navrongo, Ghana, site, Agincourt and Africa Centre, South Africa, sites and Matlab and AMK, Bangladesh sites, with major contribution of NCD mortality were cancer and cardiovascular disease (heart failure, stroke, hypertensive diseases). This finding was consistent with previous studies (76, 144, 195, 196). The rates for NCD mortality occurring before 65 years across INDEPTH sites varied over time, ranging from 1.3 per 1,000 person-years (Nouna, Burkina Faso) to 3.4 per 1,000 person-years (Africa Centre, South Africa).
Streatfield and colleagues found a significant correlation between HIV mortality and NCD mortality rates across adult populations, which are a major factor when comparing trends in NCD mortality across sites with varying HIV epidemics (196). Since according to the ICD-10 classification, cause of death should be attributed to NCDs if the HIV status is unknown and the final illness is not indicative of HIV/AIDS, this may have led to higher likelihoods that causes of death for HIV-positive people were attributed to NCDs. Tuberculosis is the most common comorbid condition of mortality related to HIV/AIDS in African sites. The contribution of diabetes and chronic respiratory disease to the overall picture of NCD mortality in INDEPTH sites was small compared to other major NCD components such as cancers and cardiovascular diseases, which may reflect risk factors not yet translating into mortality rates or some misclassification in VA methods (indeterminate cause of death).

The age-sex-time standardised mortality rates due to external causes varied across sites and age groups, with the highest rates in the Africa Centre, South Africa site (1.1 per 1,000 person-years), as described in a previous study (202). Overall, the mortality rates fluctuated with an increase and then slight downward or stable trend over time. The causes of death related to external causes were diverse, with drowning as the main cause of external cause deaths in Bangladesh (Matlab and AMK) and road traffic accidents in West and East Africa (Nouna, Burkina Faso site, Navrongo, Ghana site and Nairobi, Kenya site). In South Africa, fluctuating mortality rates were seen for external causes, with road traffic accidents and assault as the main contributors. The trends in external cause mortality observed across INDEPTH sites are in line with common expectations.

3. Transition in the Swedish Context

Sweden is a country that has achieved a late stage of epidemiological transition in the last few decades. Sweden also has good quality historical and longitudinal individual data at national level that offer a unique possibility to assess reduction in premature NCD mortality over a 15-year period. From paper III, we found that about 75% of total mortality in the 30-69 year age group during in Sweden was due to premature NCD deaths. During the 15-year period of 1991 to 2006, Sweden achieved a 26.6% reduction in premature mortality from all-causes, with around 3,000 premature deaths averted annually. The corresponding reduction in NCD premature mortality was 30.0%. Most of the deaths averted in Sweden were associated with reductions in premature cardiovascular mortality, whilst the other major component of premature NCD deaths, cancer mortality, reduced by a much smaller proportion, as reported in the recent Swedish National Public Health Report (74).

This thesis demonstrates that Sweden met the postulated target of a 25% reduction in premature mortality over a 15-year period as defined by World Health Assembly’s call, but at an earlier time, and it happened against the background of relatively good socio-economic conditions, biomedical advances and continuing population ageing in Sweden, though younger age groups benefited to a greater extent from mortality reductions. This achievement clearly demonstrates that this rate of reduction in premature NCD mortality is possible for countries at relatively late
stages of ET as in Sweden, simply as a part of continuing improvements in public health in Sweden and not done against any specific international target. Our findings imply that the WHO 25×25 target is robustly expressed in considering the unconditional probability of dying, rather than taking any other more complex endpoint. Nevertheless, achievement of a 25% reduction in a prior cohort does not necessarily mean that Sweden can attain it again for the 2010 to 2025 period, as defined in the WHO 25 × 25 target, due to different behavioural risk factor exposures across generations.

The predictive factors contributing to changes in premature mortality in the Swedish population during 1991-2006 observed in our sub study (paper III) followed our expectations that mortality rates differed between various sub-groups. Being male had a higher risk than most background factors for premature NCD death; being married or cohabiting with a partner, more educated, and employed in higher income groups were protective factors against premature NCD death, even though each group underwent its own mortality reduction transition over time. There were relatively high mortality rate ratios associated with not being employed, even after adjustment for age because the “not employed” group included many “retired” people (mostly in the 60-69 year age group) as well as those who were not employed for other reasons such as sickness. The in-migrant group also faced a considerable mortality advantage compared with those born in Sweden in earlier periods, but this difference seemed to diminish over time, which may be consistent with a “healthy migrant” effect (whereby self-selection means that migrants might be less likely to have NCDs on arrival) (203).

The changes in premature mortality are well known to be associated with changes in risk factors, not least in high-income countries such as Sweden. Since causes of NCDs are multi-factorial, and constantly associated with social determinants of health, including physical, environmental, biological, behavioural and socio-economic factors, the contribution NCD risk factors to the reduction of premature NCD death are important to investigate. Thus, life style risk factors in the past will have driven mortality reduction over time, and combined with more recent exposures, will contribute to determining future NCD mortality in Sweden. We therefore examined further how the contribution of changes in major NCD risk factors were attributable to the reduction in premature NCD mortality, using available individual data among middle-aged group in northern Sweden (paper IV). Using prospective cohort data from the VIP for 1990 to 2006, we observed downward trends in some population risk factors (smoking, hypertension and hypercholesterolaemia) that have been beneficial and significant, but the most recent 10-year changes raise in the proportions of people at risk from obesity, raised blood glucose and physical inactivity are alarming. The changes in observed risk factors varied over time, and considerably between sex and age groups. It was by no means the case that all risk factors decreased in all sex and age groups, even though there was a net reduction in both risk factors and mortality. In a public health policy perspective, this paradoxical development is a particular challenge. Some non-communicable risk factors (hypercholesterolaemia, smoking and hypertension) have been seen as manageable by health care professionals, through specific interventions that have involved the patient in concrete actions in order to achieve
specific changes. The result of these concerted efforts in Västerbotten has been successful: smoking has decreased significantly, which may be due to successful health promotion activities, including the availability of smoking cessation aid clinics, restriction in tobacco use and tobacco marketing, public smoke-free environments and health policy programmes (43, 45), as well as decreasing prevalences of hypercholesterolaemia and hypertension.

Although diabetes mortality reduced markedly among VIP participants, it accounted for a relatively small component of NCD mortality. The reduction in diabetes mortality is more likely to mirror the improvement in clinical care and support to people with diabetes over time, for both type I and type II disease, also noting that the onset of type I diabetes would not classically be related to adult risk factors. In addition, it is likely that a number of deaths among people with diabetes would have been certified as cardiovascular mortality. Meanwhile, tackling obesity and physical inactivity is seen as more difficult, perhaps because of a lack of evidence-based methods. The changes over time in the observed risk factors over time explained much of the reductions observed in premature mortality, though overall there was an increase over time in the proportion of mortality not attributable to risk factors. We found that having multiple NCD risk factors in the same individual compounded the risk for premature mortality in all categories of cause of death. Although specific risk factors may be associated with particular causes of premature mortality, as shown in Figure 11, the overall attributable contribution of observed risk factors to premature NCD mortality among VIP participants aged 40, 50 and 60 was about 33-40% during period of 1990 and 2006, and even higher for premature cardiovascular mortality.

The increasing burden of NCDs worldwide is clear in terms of epidemiological transition, together with complex mixtures of risk factors and ageing populations, causing a large increase in the numbers of the middle-aged and older people who are at increased risk of NCDs. Our study revealed that the largest premature mortality reductions were observed following reductions in smoking, hypertension and hypercholesterolaemia prevalence, as shown in Figure 10. Our results were in line with a national study from Japan, which showed smoking and high blood pressure were the greatest single factors attributed to overall adult mortality in Japan (13.4% and 10.8%, respectively) (204). Various risk factors are changing in parallel transitions, with the results that large “healthy-exposed” cohorts are developing, which will influence future burdens of NCD mortality. Worldwide, Kontis et al. projected that 37 million deaths could be averted over 15 years if global reduction targets for six NCD risk factors (tobacco use, alcohol consumption, salt intake, obesity, raised blood pressure and glucose) were achieved. Some of the largest potential premature death reductions could occur in LMICs, particularly from tobacco use and raised blood pressure (61). Sweden experienced health risk factor transition in the last few decades according to the recent Swedish National Public Health Report 2012 (74), which may be related to the ageing population, changes in cause of death composition, and changes in risk factor exposures in different geographical areas within Sweden (45, 51, 55, 58, 88). Although risk factor data from LMICs are not widely available at present, LMICs particularly in Asia and urban areas within Africa are experiencing health risk factor transitions. The observed premature NCD mortality burdens within INDEPTH sites are not that
high compared to other countries in the world, but NCD mortality will become global concern for LMICs in the future, assuming that there are not urgent effective public health actions for reducing the burden of mortality and risk factors. Therefore, having clear proof of mortality patterns is important for increasing the awareness of public health policy to reducing future burdens of mortality and morbidity in many settings.

4. Strengths and Limitations of the Studies

Paper I provides a summary of empirical evidence on how epidemiological transition theory has been applied to understand transition in specific contexts, and the process of population change (by relating mortality patterns to demographic and socio-economic trends through the development of models and mechanisms of interaction that describe the patterns, determinants, and consequences of health and disease changes in diverse populations). However, paper I has potential publication bias. Many of the published papers did not confirm the ET theory, and hence perhaps had higher chances of being accepted for publication as the utility of the theory was debated or maybe papers with more ambiguous results were never published. The use of age-standardised death rates might make the comparison across countries more convincing, though the question on the comparability of standard populations used remains valid. It is a challenge to use mortality to compare ET across countries or regions, as many factors can influence the mortality transition, which we continued to investigate in subsequent paper.

In paper II, we used INDEPTH data to mitigate the overall shortage of population data from LMICs, with a number of INDEPTH sites contributing data to the overall dataset, which have also undertaken site-specific analyses of mortality patterns that are reported separately. Some INDEPTH member countries (Bangladesh, Ghana, Burkina Faso, Kenya, South Africa) had multiple sites, which brought good opportunities to consider within-country variations and facilitate comparisons with other national sources of data. The HDSS data represent mortality patterns for complete communities, which is important in areas where most deaths do not occur in health facilities. Although causes of death determined by VA may be considered as less than ideal, this is the only feasible method for large-scale cause of death assignment in LMICs. However, there are some limitations. Assessing mortality trends over time across INDEPTH sites was challenging since individual sites reported for different time periods, even though we limited our selection to sites that had surveillance data for at least 5 years. Some misclassified causes of deaths probably happened as a result of harmonising VA data collected at many sites, over different time periods, using a variety of antecedents to the WHO 2012 standard, which was used to ensure the consistency across sites and time period as far as possible. The INDEPTH data could not explain in detail the underlying processes of mortality change more specifically with reference to causes of death, speed of mortality changes, factors that cause disruption to health, and the ways in which populations adapt to these disruptions.
Papers III and IV have the strengths of using large-scale, longitudinal data, routine register data including robust cause of death assignment in individual level for the whole Swedish population to track progress towards the WHO 25×25 target and for regional setting in assessing detailed assessments of how relevant individual risk factor exposures contribute to the population dynamics of NCD mortality through population-based measurements with high participant rates in northern Sweden, since the risk factor data cannot be addressed from the national database in Sweden. The health surveys, which are integrated into primary health care routines, target the whole middle-aged population without any selection. However, we recognise some potential limitations, for example individual risk factors changing unpredictably over time, even though it is not possible to measure them frequently on a large-scale population basis. Thus the data gathered at the VIP health examinations may not accurately reflect risk factor prevalences over the entire follow-up period. Cause of death certification is also subject to some degree of uncertainty and imprecision, but there is no alternative to accepting causes as certified. Latency periods between exposure to particular single and combined risk factors and mortality outcomes are very variable at the individual level. Other factors that might be attributable to NCD mortality, particularly for cancer, were not well covered in paper IV. Nevertheless, a large-scale dataset covering a long time period, such as this one from the VIP, helped to minimise some of these limitations.

5. Implications for Public Health and Further Research

The classical epidemiological transition theory continues in providing a useful framework for describing mortality transition experienced in all countries, although it does not completely describe transition patterns observed in all settings. The scarcity of quality mortality data from many parts of the world makes it difficult to understand the generalisability of the theory globally, as well as its interpretation. The INDEPTH Network presents to fill the scarce of good quality data in LMICs in understanding the transition processes that provide an important source of information for population health and development. However, clear understanding of mortality transition and its implications in LMICs is still hampered due to a lack of available and adequate historical and epidemiological data on morbidity and mortality, as well as the underlying mechanism of shifting the mortality transition through socio-determinants. This thesis clearly delivers message that revisions to ET theory are needed and should be based on the growing empirical evidence base in a wide range of settings. A new evidence-based formulation in terms of patterns of changes in causes of death, and disruptions in health due to emerging risks, is needed, which focuses on the underlying mechanisms and cause-specific mortality changes that result, rather than the current crude description of a decline in infectious diseases and a rise in non-infectious diseases with little reference to underlying determinants. A mutual agreement on a vital minimum dataset on civil registration and major risk factors in LMICs is need to support better documentations on epidemiological transition patterns, as well as to provide comparable health information systems in national level.
Non-communicable diseases are well-known contributing significantly to the cause of death and disability in almost all countries, in which premature NCD mortality recognised increase in the past few decades. The overwhelming burden of premature NCD mortality among older Swedish men are expected, which is likely to follow similar patterns of ET. While data from INDPETH Network showed that almost half of adults NCD deaths occurred before age of 65 years, with population-based rates in that age group being broadly similar across Africa and Asia, as well as similar to the rates in Sweden. It is important to achieve a better understanding of the patterns and underlying mechanism of NCD mortality particularly in LMICs in relation to the progress toward the World Health Assembly target for a “25% reduction of premature mortality by 2025”, since the majority of world's population is living in LMICs and they experience different stages of epidemiological transition in different spaces and at various rates. Each country needs to set different priorities depending on existing mortality patterns in order to achieve maximum benefits. Norheim et al. concluded that there were substantial reductions in mortality over the period 1970 to 2010 and was reasonably optimistic about the prospects for further global reductions (205). The finding from this thesis emphasizes the need for more action to reduce and control the increase trend of premature death, particularly in LMICs.

The achievement of the 25% premature NCD mortality reduction target in Sweden in earlier period could motivate other countries in implementing premature NCD mortality reduction programmes. Unless there are further major improvements, for example in cancer incidence or survival in the Swedish case, Sweden and other late-transition countries may not be able to reach the 25×25 target in 2025. The role of various risk factors in the disease burden has changed evidently, as shown in this thesis, which may also be related to population ageing, changes in cause of death composition, and changes in risk factor exposures in different geographical areas. Establishing health intervention programmes to reduce common modifiable risk factors (tobacco use, unhealthy diet, low physical activity and excess consumption of alcohol) are essential at the core of effective primary prevention of the main NCDs at the population level, as evidence from the VIP implemented during the last two decades. This thesis also highlights the urgent need for holistic approaches for reducing the burden of NCDs and preventing people dying prematurely in high-middle and low-income countries, through delivering appropriate health system management to the general population as well as to the high-risk individuals with emphasis on implement cost-effective action.
CONCLUSIONS

The epidemiological transition theory is still commonly used to understand the process of population change by relating mortality patterns to demographic and socio-economic trends, as shown by evidences where the theory fits the transition patterns in some countries, but with some needs for further adjustments in other settings, as well as deviations from the classical ET theory in the last four decades. The different patterns of epidemiological transition in settings with diverse background of socio-economic and health information systems in low- and middle-income countries, particularly in Africa and Asia, were revealed as clearly constituting grounds for urgent public health action. Although the current state of knowledge and evidence on historical and contemporary cause-specific mortality changes in high, middle-and low-income countries may still be too sparse to formulate a new evidence-based theory, the need to update the ET theory is clear.

In late stage epidemiological transition societies such as Sweden, the majority of deaths are unavoidably due to non-communicable diseases. The successful achievement on the 25% premature NCD mortality reduction target over a 15-year period in Sweden should be inspiring news for other countries to implementing premature NCD mortality reduction programmes through achieving the risk factor targets. The compound effects of multiple risk factors carried by individuals particularly in middle age highlight the urgent need for holistic approaches by public health agencies to address strong and sustainable efforts in developing methods to increase physical activity and combat the obesity epidemic, as well as continuing to reduce and control other non-communicable risk factors. The hazardous nature of any risk factors, but particularly multiple risk factors in particular individuals, are not problematic to conceptualise, and these messages need to be disseminated much more effectively to health professionals, their patients and the general population. Therefore, dealing with reduction in premature non-communicable disease mortality by addressing reduction of risk factor exposure is a major public health imperative.
ACKNOWLEDGMENTS

I would like to express my gratitude to my supervisors, Peter Byass, Ulf Högberg and Joacim Rocklöv, who have provided me with endless supports throughout my PhD training.

For Peter Byass, my main supervisor, who gave me the opportunity to be a part of this PhD training. He gave me a chance to grow, always helped me refine the ones I was good at and the ones that needed a little bit more work which helped me to focus on those. He challenged me to think outside the box. Thank you.

Ulf Högberg, my co-supervisor, who has always been supporting my work through his advice. Even though he is not in Umeå physically, he is always available whenever I need his guidance. Thank you for our valuable meetings and discussions. Like someone once said to missionaries who were going to a new country - preach the gospel and if you have to at times, use a few words. He uses few words and I have learned immensely from him.

My heartfelt gratitude goes to Joacim Rocklöv, for his statistical guidance. He endorsed me to grow in my position, by consistently making me feel like I was part owner. He always there to guide me through the process.

I am indebted to Lars Weinehall, my examiner and past head of the Epidemiology and Global Health Unit, who has provided me the opportunity to undertake this PhD training, and for being supportive academically and socially. I have learnt so much from all of you.

My due thank to the Unit of Epidemiology and Global Health (Anneli Ivarsson and the leadership team) for the great opportunity to register and do my PhD in this active and international research unit. I express my gratitude to the Umeå Centre for Global Health Research for supporting my PhD training. I am also thankful to the Graduate School for Population Dynamics and Public Policy (Johan Lundberg), within the Ageing and Living Condition Program (Gunnar Malmberg and Anders Brändström), now the Centre for Demographic and Ageing Research at Umeå University, which gave me the possibility to access and explore the rich Linnaeus data. As a student in the graduate school, I have been supported in learning new knowledge and skills, as well as expanding my network, through discussion and collaboration with other researchers from multidisciplinary research areas.

My tutors and co-authors, Stig Wall, Lars Weinehall, Margareta Norberg and Edward Fotrell who shared their constructive ideas and collaborated with me during the write-up of my papers. You all have been a great support.

I am also very grateful for the helpful comments and valuable suggestions provided by Anneli Ivarsson, Urban Janlert, Göran Broström, Lennarth Nyström and Fredrik Norström in my PhD planning and evaluation process. My deepest gratitude goes to Anna Karin Hurtig and Klas-Göran Sahlen for supporting me when life was up and down. Lars Lindholm and Miguel San Sebastian for sharing your knowledge and experiences. Thanks for your support.
Hans Stenlund and Ann Öhman, and Professor Mohammad Hakimi from Gadjah Mada University, Indonesia who had supervised me during my master training, which gives me a strong foundation to continue with this PhD study.

My heartfelt gratitude goes to my colleagues at the graduate school: Johan Lundberg, Eva Palmquist, Petra Sanberg, Sofia Tano, Daniel Eriksson Sörman, Lukas Gorniok, and Markus Nyström for giving good moments and suggestions.

I am also deeply grateful to all staff in Unit of Epidemiology and Global Health: Karin, Birgitta, Ulrika, Veronika, Carolina, Lena, Susanne and Andreas for being very support in different aspects throughout my training, as well as for sharing your friendship and love and making me feel homey. Göran Lönnberg and Wolfgang for your excellent IT supports. Now I know the minimum distance of my coffee cup and my computer should be at least 5 metres. My incredible roommates (Helene, Lotta and Kjerstin D), with whom I have shared laughter, cries and smells (*censored*), as well as our 25m2 incubator space during the last 4 years.

All my colleagues within the Epidemiology Unit, among whom: Malin, Curt, Barbara, Elisabet, Mojgan, Fredinah, Julia, Masoud, Trang, Kristina L, Maria Furberg, Elisabeth, Linda, Raman, Isabel, Alison, Katja, Lena BO, Tesfay, Gladys, Juan-Antonio, Mariano and Claudia, and many others for your friendships, companions, and intellectual supports.

I thank for Jennifer and Brian Williams for loving friendship, since we met in Newcastle, Australia. Your support and companionship will always be remembered.

My gratitude also goes to my Indonesian friends (Nurul, Trisasi, Elli Hayati, Fatwa, Ari, Utami, Kurnia Lestari) who always support me all the time through their friendship. Without their friendships and supports during my doctoral journey, I would not have been able to complete this work.

Karin and your lovely daughter Maria, for being lovely friends, and being very generous in sharing “life and “❤️” so I can move on. Thank you for being my companion.

I give my special thanks to Birgitta and Kenneth Åström for being our Swedish family. You have shared your friendship ever since I knocked on your hotel room door in Puri Artha Hotel, Yogyakarta in 2003. Thank you both from the bottom of my heart.

I thank my husband, Nawi Ng, and daughters, Michelle Andra and Chrysella Marlyn, for loving me endlessly and providing encouragement in many ways. Their love and support are most evident when they tried to cheer me up when life goes up and down. I also thank my family in Indonesia, especially my parents who always support me with their love and wisdom. They have always listened to my thoughts and challenged me to achieve more. Thanks for your everlasting parental love.

Above all, I especially thank and give gratitude to God because in the day when I cried out, God answered me, and made me bold with strength in my soul (Psalm 138:3).
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