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ISSUES OF VALIDITY IN LONGITUDINAL STUDIES OF YOUTH TOBACCO USE

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To observe, you must learn to compare,
to compare, you must have observed.
By observing, knowledge is formed,
while knowledge is required,
to be able to observe.

Bertold Brecht (1898-1956)

In Memory of
Efraim Engström
My Grandfather
ABSTRACT

In the Stockholm region, a prospective longitudinal study: BROMS Cohort Study (Children’s Smoking and Environment in the Stockholm County) was conducted between 1997 and 2005, with the primary aim to investigate determinants of adolescents’ tobacco use. It was based on a sample recruited in schools with junior high grades. This thesis highlights issues of validity in cohort studies based on samples of children and adolescents. Research questions of interest were: determinants of participation at the school, family and individual levels; validity of reports of smoking and snus use among adolescents; methods for assessment of symptoms of nicotine dependence among adolescent tobacco users; stability of retrospective recall of smoking during pregnancy among the adolescents’ mothers. All papers in this thesis are based on data from the BROMS Study.

At the school level, the socio-economic characteristics of the area, the size of the schools, but not the presence of a tobacco policy predicted school participation. At the parental level, education and average social status in the residential area was associated with parental consent.

At the level of the adolescents, the attrition over 7 years follow-up was low as only 6% of the subjects dropped out of the study permanently, and the proportion participating in all follow-up surveys was close to 70%. Many psychosocial traits and behavioural factors beside tobacco use predicted lack of sustained participation. Significant predictors were: male gender, an increasing number of recent stressful events, most of them connected with unstable family conditions, school truancy and low school performance. In a sub-sample of 520 adolescents at aged 15 years, self-reports of cigarette and smokeless tobacco (snus) use were compared with saliva cotinine concentrations (cut-point of 5 ng/ml). Overall, the concordance between self-reports and saliva cotinine levels was high. Disagreement was found in subjects reporting occasional, infrequent or irregular tobacco use.

At the age of 17 years, lifetime experience of nicotine dependence and withdrawal symptoms were reported by 466 exclusive smokers, 209 exclusive snus users and 144 dual users. A significantly higher proportion of dual users and exclusive snus users reported symptoms of nicotine dependence (withdrawal excluded) compared to exclusive cigarette smokers. Dual users reported the highest frequency of most withdrawal symptoms. Craving for tobacco was the most frequently reported withdrawal symptom among all types of users.

Overall high stability and consistency of retrospective recall of smoking during pregnancy by the adolescents’ mothers was found when this was compared with reports given by the same mothers at the time of their pregnancies as recorded in the Swedish Medical Birth Registry. Discrepancies were more frequent among women with low-level pregnancy smoking and among women who had changed their smoking behaviour over time.

In summary, participation of schools and families in longitudinal studies involving youths cannot be predicted in a straightforward way as determinants of participation differ at the organisational and individual level. Hence, consideration on selection bias and generalisation must take into account study-specific hypotheses. Retrospective recall of smoking in pregnancy is reliable, but instability of recall is likely to occur for low-level or irregular smoking. Self-reports of current tobacco use in mid-adolescence are reliable, when elicited through questions that take into account the specific patterns.
of tobacco use in adolescence, as was the case in this cohort study. Smokeless tobacco use in adolescence is associated with symptoms of nicotine dependence at least as frequently as cigarette smoking is. Young tobacco users who combine smokeless tobacco with smoking obtain particularly high scores on scale items assessing nicotine dependence. In longitudinal studies of youths, baseline psycho-social characteristics of the study subjects can be used to predict, thence to prevent or minimize losses to follow-up.

Keywords: cohort, validity, smoking, smokeless tobacco, adolescents, participation, consent, retrospective reports, nicotine dependence, attrition.
LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


IV Post A, Gilljam H, Rosendahl I, Bremerg S, Galanti MR. Symptoms of nicotine dependence in a cohort of Swedish youths: a comparison between smokers, smokeless tobacco users and dual tobacco users. In manuscript

V Post A, Gilljam H, Bremerg S, Galanti MR. Psycho-social determinants of attrition in a longitudinal study of tobacco use in youth. In manuscript

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# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BROMS</td>
<td>Children’s Smoking and Environment in the Stockholm County</td>
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<td>CAN</td>
<td>Swedish Council for Information on Alcohol and Other Drugs</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>e.g.</td>
<td>for example</td>
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<tr>
<td>ESPAD</td>
<td>European School Survey Project on Alcohol and Other Drugs</td>
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<tr>
<td>HONC</td>
<td>Hooked on Nicotine Checklist</td>
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<tr>
<td>MBRS</td>
<td>Swedish Medical Birth Registry</td>
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<tr>
<td>mFTQ</td>
<td>Modified Fagerstöm Tolerance Questionnaire</td>
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<tr>
<td>n</td>
<td>number</td>
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<td>ND</td>
<td>Nicotine dependence</td>
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<tr>
<td>ng/ml</td>
<td>nanograms per milliliter</td>
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<td>NTS</td>
<td>Swedish abbreviation of Nationalföreningen för upplysning om tobakens skadeverkningar, National Smoking and Health Association</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>p</td>
<td>Probability value</td>
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<tr>
<td>PNR</td>
<td>Personal Number, the Swedish social security number</td>
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<td>SCB</td>
<td>Statistics Sweden</td>
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<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>UNCR</td>
<td>United Nations Convention on the Rights of the Child</td>
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<tr>
<td>Visir</td>
<td>Swedish abbreviation of Vi som inte röker, We who do not smoke</td>
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<td>vs.</td>
<td>versus</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WHO CIOMS</td>
<td>WHO Council for International Organizations of Medical Sciences</td>
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<td>WHO FCTC</td>
<td>WHO Framework Convention on Tobacco Control</td>
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1 BACKGROUND

In Sweden, 27% of men and 17% of women in the age group 16-84 years smoke and/or use snus (Swedish oral tobacco) on a daily basis. However, there are major age, gender and regional differences in the use of tobacco. The prevalence of smoking in urban areas is lower than in the country as a whole, while snus use is more prevalent in the northern part of Sweden.  

1.1 SMOKING IN THE ADULT SWEDISH POPULATION

In Sweden, cigarettes dominate the market of inhaled tobacco products. Daily smoking rates have fallen since the late 1970’s by roughly 1% per year in males and by 0.5% per year in females and Sweden was the first country to reach the World Health Organization’s (WHO) goal of prevalence of adult daily smoking below 20%. Nonetheless, smoking is still one of the most important causes of disease and premature death in Sweden.  

The prevalence of daily smoking is higher among adult women than men, 14% vs. 11%. A population-based study conducted in southern Sweden reported that the gender difference of daily smoking is largest among subjects 18 to 24 year-old. Smoking rates also varies between different social groups. The highest prevalence of daily smoking is seen among early retired individuals, the long-term unemployed, the less educated, single mothers and among males born abroad. The prevalence of occasional smoking is rather high 11% in both genders.  

1.2 SNUS USE IN THE ADULT SWEDISH POPULATION

Snus is the other widely used tobacco product in Sweden. Snus consists of finely ground tobacco and salt with high moisture (35-60%) and alkaline pH (7.8-8.5). As in cigarettes, nicotine is the addictive component in snus and its content varies between 0.5% and 1.3% according to brand. The user places the product under the upper lip as a “moulded” pinch or as a sachet (looks like a teabag). The pH in snus can be manipulated by the manufacturers in order to increase or decrease nicotine absorption through the oral mucosa and as a result the exposure to nicotine is likely to be high and more prolonged than that occurring after cigarette smoking. The plasma nicotine levels from smokeless tobacco are comparable to those typically found after smoking, the main differences being the absence of a rapid peak and the slower decline of concentration (Figure 1).
Smokeless tobacco has a long tradition in Sweden as a traditional habit among male manual workers. In the end of 1960s, snus use increased in popularity due to product development and aggressive marketing. In 1973 portion-packed snus was launched and rapidly gained popularity, bringing the number of users to the present 0.8 million daily snus users in Sweden. The use of snus has crossed the gender barriers as women now account for about one fifth of all snus consumers. The consumption of snus has increased steadily in both sexes over the last 3 decades and only recently showed a slight decline among men. In 2008, 19% of the men aged 16-84 years used snus daily vs. 4% of the women of the same age. The highest rates were recorded among men 30-44 years (23%). Daily snus use is more common among both men and women in rural areas and among women in urban areas. The health effects of prolonged snus use are incompletely known, since there are only few studies conducted in the Swedish population. However, based on the available evidence, a report issued by the Swedish National Institute of Public Health reached the conclusion that the use of snus has serious health effects. In the absence of solid evidence for the exact role played by the availability of snus for the declining trends of cigarette smoking in Sweden, a heated debate has emerged. Some insists that snus has played a significant role in reducing smoking whereas other argue that the role of snus has been exaggerated.

1.3 USE OF TOBACCO AMONG PREGNANT WOMEN IN SWEDEN

In Sweden, the proportion of women who smoke daily in the first trimester of pregnancy decreased for all ages from 31% in 1983 to 7.5% in 2006 (Figure 2).
Figure 2 Daily smoking in early pregnancy (%) 1983-2006. Reproduced from the Swedish Medical Birth Registry.

The prevalence of daily snus use in early pregnancy has been constant around 1.4%, since the time it was first recorded in 2000. But there are regional differences and among women in the northern part of Sweden a prevalence of 3.6 to 6.9% have been reported. The increased popularity of snus among young women has become a matter of concern because of adverse fetal effects of snus use in pregnancy.

1.4 TOBACCO CONTROL AND PREVENTION IN SWEDEN

In 1964, Sweden was one of the first countries to earmark government funding for public information about the harmful effects of tobacco. Information on tobacco was spread by Visir and NTS, two politically active NGO’s. A new NGO, A Non Smoking Generation, was established in 1979 with the purpose of changing attitudes to smoking among youths. In 1983, the first guidelines to limit smoking in public places were launched. The Swedish National Institute of Public Health was established in 1992 and began a nationwide effort to prevent the effects of tobacco use. The Institute has supported NGO:s such as Health Professionals against Tobacco, to raise public support through coordinated actions.

The Swedish Tobacco Act was adopted in 1993, replacing earlier legislation on health warnings and a partial ban on advertising. As of July 1st, 1994, the law was strengthened by prohibiting most types of tobacco advertising and banning the sales of packs containing less than 20 cigarettes. An age limit of 18 years for the purchase of tobacco products went into effect on January 1st, 1997. In 1998 the Swedish smoking cessation telephone helpline (Sluta-Röka-Linjen) was launched. A smoking ban including restaurants, pubs, bars and cafés was enacted in June 1st, 2005.

As knowledge about the harmful effects of tobacco has deepened, the attitudes towards tobacco have changed. Today, unlike in the early 1990’s, it is generally accepted that workplaces and public spaces are smoke-free areas. In 2005, the Swedish Government ratified the WHO Framework Convention on Tobacco Control.(WHO FCTC) The public health community strongly supports the implementation of the convention.
1.5 TOBACCO USE AMONG YOUNG PEOPLE IN SWEDEN

Since 1971, the Swedish Council for Information on Alcohol and Other Drugs (CAN) conducts national surveys of tobacco use among students in the 9th grade of compulsory school (age 15-16 years). Smoking was more common in the early 1970’s with approximately 40% in both sexes. In 2008, 22% of boys and 28% of girls reported any smoking, and 8% and 11% respectively, reported smoking on a daily or almost daily basis. However, a rapid increase in the uptake of smoking seems to occur during the first two years after compulsory school. In fact, the prevalence of smoking among students in senior high school (age 17-18 years) in 2008 was 34% among boys and 41% among girls, while girls 12% and 18% respectively smoked daily or almost daily. Among 9th grade students in 2008, 16% of boys and 4% of girls reported that they used snus on a daily or almost daily basis. For the boys, this means that the proportion of snus users has returned to the level seen in 1997 after a temporary increase. Snus use in girls increased steadily from 1997 to 2006, but in the past 2 years it has fallen slightly.

Figures 3 and 4 show the trends in smoking and snus use among 15-16 years old between 1983 and 2008 in Sweden.

Figure 3 Prevalence of current smoking (%) in the 9th grade by gender. Reproduced from CAN Report 114, 2008.
In 2003 the ESPAD (The European School Survey Project on Alcohol and Other Drugs) survey collected data from 7 countries (France, Greece, Italy, Latvia, Poland, the Slovak Republic and Sweden) among students aged 17-18 years. The prevalence rate of lifetime smoking 40 times or more was highest in Latvia, the Slovak Republic and Greece where over 40% of the students fulfilled the criteria. The lowest rate was found in Sweden (33%), as was the rate of smoking during the past 30 days. In 3 countries, boys reported a higher rate of smoking than girls (Latvia, Poland and the Slovak Republic). In the 3 Mediterranean countries gender differences were small. 22

Although youths’ smoking prevalence in Sweden is lower than in most countries it is of concern that Swedish girls start smoking at an earlier age compared to girls in other European countries. 23

1.5.1 Initiation of tobacco use among youths

The development of tobacco use and dependence in young people is a complex process. In western countries, regular use of cigarettes and smokeless tobacco is usually established before the age of 20. 24 The traditional descriptive model of progression to dependence recognizes discrete stages from initial trying through experimentation and regular smoking. 25 However, recent studies have challenged this model suggesting that the onset of nicotine dependence (ND) among smokers may be closer in time to initiation than previously thought (Figure 5). In an American study, early symptoms of ND appeared within days to weeks from the onset of occasional use, often before the onset of daily smoking. 26 Also, the time interval between experimental and daily use of cigarettes is characterised by multiple transitions, involving both progression and regression in frequency and intensity. 27 Whether the developmental trajectory of smokeless tobacco use has similarities with that of cigarette smoking is not entirely clear, although a recent Swedish study has demonstrated that three trajectories during adolescence are common in both tobacco types, involving a) a protracted experimental stage, b) a slow escalation and c) a rapid escalation to a level of daily use. 28
1.6 PREDICTORS AND DETERMINANTS OF CIGARETTE SMOKING INITIATION AND PROGRESSION

Three broad classes of determinants for smoking in adolescence have been identified at the individual level: psychosocial characteristics (such as gender, pro-smoking attitudes, self-esteem, academic achievements); family influences (parental smoking, number of smokers in the family, parental permissiveness and approval); peer-influences (number who smoke, peer relations). Gender differences exist not only in smoking rates but also in the timing of uptake and progression, with earlier initiation among boys but a more rapid transition to advanced stages of smoking among girls.

Adolescents’ smoking initiation, as well as progression to regular use is correlated to a number of psychosocial characteristics such as low self-esteem, low self-efficacy and lower educational aspirations, externalising behaviours and anxiety/depression. Parental socio-economic status and education are generally inversely correlated with children’s smoking. It has been shown that parents serve as role models and that their habits may influence the choices made by their children. Also, parental tobacco use is associated with a more rapid escalation of tobacco use among their children. Smoking is more frequent among children who dislike school and play truant. In Sweden, students in vocational secondary school programs are daily smokers twice as frequently compared to pupils in theoretical programs. Recent studies point towards the importance of early life and pre-natal risk factors for smoking progression and dependence but methodological problems hamper the interpretation of these findings.

1.6.1 Predictors and determinants of smokeless tobacco use initiation and progression

In contrast to a plethora of studies regarding smoking, the knowledge about initiation and progression with smokeless tobacco is sparse. There are few studies based on adolescent samples, and even fewer employing a longitudinal design, which is crucial to understand the temporal sequencing of behavioural disorders and to infer causality. Male gender is a main predictor of smokeless tobacco use in many countries. Apart from this gender difference, risk factors identified for smokeless tobacco use do not differ from risk factors for smoking, such as parental, siblings’ and friends’ use of smokeless tobacco as well as a favorable attitude to the product. In Sweden, snus use among male adolescents has gained popularity in some subgroups, e.g. among hockey players where environmental factors may play a promoting role.
1.6.2 Assessment of nicotine dependence in youths

Brain exposure to nicotine results in dependence in a substantial proportion of users, and dependence is the main reason for continued use of tobacco. Dependence from nicotine is similar to that from other psychoactive drugs, resulting in physical and neurobiological withdrawal symptoms during periods of interrupted use. Common symptoms of psychological tobacco withdrawal are: irritability; difficulty in concentrating; anxiety; restlessness and physical symptoms such as dizziness; vivid dreams; mouth ulcers and cough. When abstaining from tobacco, adolescent smokers report withdrawal symptoms similar to those of adult smokers.

Progression to nicotine-dependent smoking has been conceptualised as proceeding sequentially over 2 to 3 years through 5 stages, including the preparatory, trying, experimentation, regular use and dependent stages. Regular tobacco use has been considered necessary for ND to develop. Despite this, later research showed that symptoms of ND in adolescents can develop soon after initiation. This raises the question of how and when symptoms of ND and withdrawal manifest itself in youths. While there are quite a few studies of adolescent ND in smoking, progression to dependence in young smokeless tobacco users has not hardly been studied at all. One of the reasons behind this inadequate knowledge may be the lack of suitable instruments to assess ND from smokeless tobacco. However, some attempts have been made with adult populations, such as the adaptation of The Fagerström Test for Nicotine Dependence to smokeless tobacco users (FNTD-ST). In order to gain insight into the natural history of adolescent ND, future research should look for developmentally appropriate instruments that also are suitable for assessing dependence in users of smokeless tobacco and dual users.

Summary: Smoking in Sweden has steadily declined during the last four decades while smokeless tobacco use has gained popularity. Changing patterns of tobacco use and of corresponding attitudes pose methodological challenges for research in this domain, especially concerning studies on youths.
2 METHODOLOGICAL ISSUES IN LONGITUDINAL STUDIES OF TOBACCO USE AMONG YOUTHS

2.1 COHORT STUDIES

In order to identify risk or protective factors for a disease it is essential to carry out longitudinal epidemiological studies. In a cohort study, a group of individuals are observed at two or more points in time. The observations of subjects may have several purposes, a descriptive one (measuring the occurrence of the event of interest) and an analytical one (measuring the association between an exposure or presence of risk factor and the outcome event). In an analytical cohort study, subjects who share the presence of a risk factor or risk predictor (exposed) are compared with those who do not (unexposed). Unlike case-control studies, the information on exposure is collected independently from the occurrence of the outcome, and it is possible to study multiple effects from a single exposure.\textsuperscript{55}

Cohort studies are useful for studying exposures where randomised controlled studies are not feasible, be it for instance ethical reasons, as is the case for cigarette smoking. As in all observational studies, even in well-conducted cohort studies, the inference on a causal relationship between a risk factor and a disease may be difficult. In fact, exposed and non-exposed subjects may differ in other characteristics that affect the outcome of interest (confounders). A major problem in prospective cohort studies is the long time needed for the condition of interest to develop. Beside retention problems, long observational time also implies that repeated assessment of time-varying exposure is often necessary, which entails high costs of these studies.\textsuperscript{56, 57}

Cost-efficiency may be increased by conducting studies with retrospective cohorts. A retrospective (historic) cohort study is different from a prospective cohort study, concerning the position of the investigator with respect to the person-time experience of the cohort. In a retrospective cohort study, data are collected from past records, contrary to a prospective cohort study where study time and person-time experience of the recruited subjects are concurrent. However, the presence of adequate information in pre-existing records, such as medical records, should be carefully assessed as this information is usually collected for purposes different from the specific research question.\textsuperscript{58} In Sweden for instance, smoking behaviour is recorded in only few population-based registers which allow individual identification. Examples of such registers are the Medical Birth Register (MBRS),\textsuperscript{59} and the Swedish Conscripts’ database.\textsuperscript{60} A prospective design also allows for more precise measurements of exposure and of potential confounding factors.

Subjects in a cohort at the time of recruitment are usually linked in some way, for instance a defined age group, a significant life event (e.g. pregnancy), a geographical location or place of employment, etc. In tobacco studies, there are 2 well known examples of large and long-lasting cohort studies. The British Doctors’ Study, a seminal prospective cohort study encompassing 34000 male doctors followed from 1951 until 2001. This study provided convincing statistical proof that tobacco smoking increased the risk of lung cancer.\textsuperscript{61} The Swedish Twin-Registry, started in 1961, consists of several birth cohorts presently including 172000 twins. Analyses from these cohorts convincingly showed that the increased risk of lung cancer amongst smokers could not be explained by genetic factors.\textsuperscript{62}
2.2 EPIDEMIOLOGICAL STUDIES OF YOUTHS

2.2.1 Recruitment settings

Behavioural patterns such as physical activity, nutrition and smoking initiation constitute risk factors operating at young age that may cause significant morbidity or mortality later in life. Therefore, there is a growing interest for epidemiological studies involving children and young people. Recruiting subjects at birth is not uncommon. In Europe, several birth cohort studies designed to study asthma and atopic diseases have been enrolled over the last two decades. The Swedish “Bamse” cohort study and the German “Lisa” cohort study, both involving 4000 children are such examples. However, accruing and following up cohorts based on children and adolescents is more difficult than tracking adults. Therefore, the risks of loss of statistical power and of selection are common problem. For instance, studies in urban settings or studies on newborns recruited only from university hospitals may not be representative of the general population.

School-based recruitment of youths is considered a highly efficient way to reach young populations in studies that involve risk factors with onset during late childhood and adolescence. However, non-participation of entire units (i.e. schools and classes) may cause drop-out that is more substantial and selective than that occurring at the individual level. Methods for maximising students’ participation in school-based research have been summarised as pertaining to 3 processes: communication, logistics and incentives. Communication includes individualised presentation of information at different levels of the target group, as well as methods to facilitate access to the investigation instruments in order to increase the coverage of the target. Logistics include the way invitation is addressed and how reminders are optimized. The use of different kind of incentives at the school-level can improve the recruitment process.

Social cognitive models primarily influenced by social learning theory, have been employed to improve the recruitment process at the organisation level. The theory postulates that 3 factors are of importance in the decision-making process of the organisation’s participation in a given research project: the decision-makers own beliefs and self-efficacy in implementing the project; the credibility of the investigator; the purpose of and resources for the project, including outcome expectation. Taking these factors into consideration at the beginning of a study can facilitate effective recruitment and retention of organisational units such as schools, thus preserving the integrity of the study design.

2.2.2 Informed consent

The Declaration of Helsinki is a universally applicable document for ethical research. Consent is necessary in epidemiological studies that use personally identifiable data. Informed consent is given by a person who understands the purpose and nature of the study, what participation implies and what risks and benefits are intended to result from the study (WHO CIOMS). Youth studies pose particular problems concerning meaning and ways of obtaining informed consent. Children’s rights are laid out in the United Nation convention on the rights of the child (UNCRC). Consequently, research involving children under the age of 18 years (if not legally competent at earlier age) requires consent from both the child and the parent. Two strategies are possible in order to obtain parental consent in epidemiological studies, i.e. through active (often written) vs. passive (assumed) consent. Compulsory written parental permission may dissuade some youths from participating. Also, the process of obtaining consent may promote parent-child discussion of sensitive issues. Therefore, it is important to consider minors’ capacity for decision-making based on their cognitive function.
authors view passive parental consent (have to decline their child’s participation) as a way of minimizing selection bias and drop-out at recruitment. Selection may lead to under-representation of important groups such as ethnic minorities and socio-economic vulnerable parents. Others claim that active consent allows for better compliance at follow-up. In school-based research, high rates of active parental consent can be obtained, through innovative methods e.g. financial compensation to schools for efforts during the consent procedures, similar to that of assumed consent. However, the opportunity of specific strategies of informed consent involving minors rests on the purpose of the study and its anticipated benefits vs. hazards, which are to be ultimately evaluated by the Ethical Boards at each university.

2.2.3 Retention

Longitudinal studies with repeated measurements of exposures or outcomes from the same subjects over a long time pose problems of retention of the study population. Retention involves several steps. First, subjects have to be traced during the follow-up period in order to assess their vital status and other characteristics of interest for the study. Population registers containing personal identifiers such as name, birth date and last known address are commonly used. Second, compliance to the study requirements has to be maintained over time. Factors facilitating or hindering adolescent participation in research fall into 4 classes: demographics, individual factors, family characteristics and logistical factors, such as frequent changes of residence. Methods for reducing the impact of attrition have been proposed: collection of data at school, tracking absentees by postal questionnaire, telephone or home interviews. Payment and rewards have also been used, although whether incentives are useful as retention method is unclear. On the other hand, it does not seem that the medium of data collection has a decisive impact on response rates as shown by studies comparing web form and paper form to collect information on alcohol and tobacco use among students.

Even with efficient tracing and high compliance, longitudinal studies with fixed cohorts tend to lose participants (attrition). This is mostly due to logistical factors such as change of address or telephone number, particularly relevant for young urban populations. Attrition can cause selection of the study population and ultimately biased results. For instance, it has been repeatedly shown that youths who are prone to drop-out are more likely to come from a single-parent household, to be less successful in school and to more often be substance users. However, very little is known about psychosocial characteristics of drop-outs during the course of follow-up in tobacco studies in youths.

2.2.4 Reliability of information

In epidemiological studies, questionnaires or interviews are common instruments to obtain self-reports of characteristics or events in the study population that cannot be directly observed as is the case for tobacco use. To ensure reliability of self-reports, standardized questions coupled with pilot testing are common ways to ensure valid and reliable results. Four processes intervene in a question-and-answer process: comprehension, retrieval, judgment and response. Comprehension refers to the ability of the responder to understand the question being asked and is critical for data quality. The information being sought is often difficult to be recalled accurately (such as dates and frequencies), thus judgment intervenes to interpret the requested information and adapt the answer. Finally, the format of the response alternatives and editing may affect the survey results. Intuitively, the steps described above rely on cognitive and manual skills that may be incompletely developed during childhood and adolescence.
Reliability also depends on the variability of the tools on which the test is based, the variability of the method of measurement and the skill with which it is administered. Reliability of self-reports has a profound impact on the validity of the intended measurement, i.e. the ability to capture the entire distribution of the characteristic or event of interest (sensitivity), excluding spurious events (specificity). In other terms, sensitivity measures the proportion of people identified by the instrument as having the characteristic under study among all those who are actually positive for the characteristic itself. Specificity measures the proportion of negatives at the characteristic under study which are correctly identified as such by the instrument. Sensitivity and specificity of an instrument are usually measured against another measurement treated as “gold standard”, for instance another source of information or a biological marker. A review of the reliability of adolescents’ measures of cigarette smoking use against biological markers has concluded that adolescents’ reports show generally high validity, especially when anonymity is ensured. Whether this is true also for smokeless tobacco use is not clear. In addition, unfavorable social norms and enforcement of environmental measures to control tobacco use may deeply modify the trustfulness of self-reports.

2.3 PURSUING VALID INFERENCE IN COHORT STUDIES OF YOUTHS

2.3.1 Validity in epidemiological studies

When discussing validity of results in epidemiological studies, it is customary to distinguish between external and internal validity. The former term refers to the possibility to generalize the study results to other populations than the specific study sample. External validity is of major concern in descriptive studies, where the primary goal is to infer the frequency and distribution of some characteristics or events in the population. Large, randomly selected representative samples with low or random loss of information are thought to provide valid estimates of the occurrence of the traits under study. Conversely, large and selective drop-out may undermine the external validity as the characteristic of interest may be differently represented between those who were recruited into a study and those who were not.

For instance, a cohort study conducted to describe the incidence of daily smoking in a young population will likely underestimate the real incidence of this behaviour, as lost to follow-up are more likely to belong to population subgroups where the risk of taking up smoking is high (e.g. socially disadvantaged groups). Internal validity, on the other hand, refers to the lack of systematic errors in analytical studies in making inference about the presence and magnitude of an association between a risk factor for (or a predictor of) an outcome and the outcome itself. In cohort studies, threats to internal validity may come from processes that affect the assessment of the outcome differently among those exposed and those non-exposed to the risk factor of interest, from errors in assessing the exposures or from confounding, i.e. from the effect of factors that may by themselves cause the outcome of interest and have a different distribution between exposed and non-exposed. The most feared invalid (biased) results are those that manifest as departure from the null hypothesis of no association when this latter is indeed true (for instance a spurious protective effect of an intervention or a spurious detrimental role of a biological exposure). However, the reverse is also frequent, i.e. the results do not consent to reject a false null hypothesis. In cohort studies involving young people the following threats to internal validity may be of particular importance.
2.3.2 Selection bias

Selection bias in a cohort study may occur when exposed and non-exposed subjects are differently recruited into a study in dependence of their probability to develop the outcome of interest. 90 In population-based studies, it has been frequently observed that subjects from socio-economically disadvantaged groups are less prone to participation than people with high income and/or high education. 91 This is also the case for enrolment of youths, as participation involves family’s consent and compliance which is generally lower in socially deprived groups. 92 Even when the family’s compliance is assured, other factors in the social environment may concur to selection as shown in a recent school-based study where teachers’ and children’s participation was lower in socially deprived areas. This was also true for the risk of partial non-response in children. 93

However, self-selection does not necessarily imply the presence of a bias unless the circumstances intervening on selection were differently linked to the outcome under study among participants compared with non-participants. 94 For instance, in a study of influence of parental socio-economic status on offspring’s smoking behaviour participating parents from socially disadvantaged groups may be particularly health-conscious and endorsing “protective” attitudes and behaviours towards children’s smoking while this would not be true among medium-high income families. This would result in an underestimation of the adverse effect of low parental socio-economic status on children’s smoking.

Being able to make assumptions on factors that may influence selection and on the direction of the selection itself is important for drawing valid inference from the data.

2.3.3 Misclassification of exposure or outcome

Misclassification of exposures or outcomes is a threat in all epidemiological studies, but is particularly frequent when subjects are asked to self-report the events of interest. Among young people, incorrect self-reports may be given because of different reasons. Purposeful alteration is likely when traits or behaviours under study are surrounded by social approval or rejection or subjectively perceived as desirable/undesirable. 95 For instance, it has been repeatedly shown that adolescents tend do underestimate their weight and overestimate their height. 96 In countries like Sweden where a comprehensive Tobacco Act has been implemented and the prevalence of cigarette smoking in the adult population is declining, it might be particularly sensitive for teenagers to report smoking cigarettes. Imperfect recall of past events may also lead to misclassification. 97 Unawareness of the specific information being requested may lead to misclassification. For instance, surveys have shown that children and adolescents are not able to classify correctly their parents’ education. 98 Finally, assessment instruments which are not tailored for the specific age group may induce responses that do not correctly classify the subject’s experience. For instance, questions used for the assessment of smoking behavior among adults usually assume daily smoking, and would misclassify young experimental smokers as non-smokers. 99 Misclassification that occurs independently for exposure/predictors and outcomes (non-differential misclassification) usually introduces a bias that is predictable in its direction, i.e. towards the null hypothesis of no-association. However, there are exceptions and even non-differential misclassification can bias the results. 57 This latter is invariably the case when differential misclassification occurs. For instance, children to non-smoking parents may be less prone to report early experiences with smoking perceived as disapproved, thus inflating the “protective” effect of non-smoking family influences.
Summary: Prospective cohort studies of youths pose several methodological and practical challenges, including ethical issues, strategies for recruitment and retention, and choice of instruments for collection of reliable information.
3 SUBJECTS AND METHODS
The BROMS Cohort

3.1 PURPOSE OF THE STUDY
The BROMS Cohort Study (Swedish acronym for Children’s Smoking and Environment in the Stockholm County) was established at the Tobacco Prevention Unit of the Stockholm Centre of Public Health, Stockholm County Council. All papers included in this thesis are based on this prospective longitudinal study conducted between 1997 and 2005, the main purpose of which was to gain knowledge on determinants of tobacco use throughout adolescence. Of particular interest were questions related to subgroups (gender, nationality), to emerging patterns of tobacco use (prolonged occasional use), to smokeless tobacco products (snus), and to factors amenable of community based prevention (e.g. purchase accessibility, school policy and education, media-based information). The BROMS Cohort Study was approved by the Karolinska Institute Ethical Board at Huddinge University Hospital, record nr. 10/97.

3.2 RECRUITMENT OF THE STUDY SUBJECTS
A random sample of all schools with intermediate grades in Stockholm County (approximately 20,000 pupils) was selected. Schools with other language of instruction than Swedish were excluded. Cluster sampling with a probability to be included proportional to school size (number of pupils) was employed in order to avoid overrepresentation of small-size schools. The initial sample consisted of 118 schools encompassing 6,294 children in the 5th grade. The headmasters were formally asked to facilitate the recruitment of the study participants. A total of 91 schools (77% of the initial sample) accepted the invitation, 20 (17%) declined and 7 (6%) did not respond after 4 reminders.

Parents (including guardians) of the children in the consenting schools were asked to provide written permission (active consent) for their children's enrolment in the cohort. Non-responders were contacted with three mailed and one telephone reminders. Particular efforts were undertaken to reach parents in school areas with high share of immigrants. Parents’ permission to participate in the study was granted for 3,050 out of 4,671 eligible children (65%).

The baseline assessment was completed by 3,020 students (1,537 boys and 1,483 girls) out of the 3,050 with valid parental (including guardians) consent (48% of the initial sample), who therefore constitute the study cohort. Drop-out among 30 students with parental consent was caused by: refusal (n=19); return of an empty or unreadable questionnaire (n=9); absence from school during the period of data collection (n=1); moved and not further located (n=1).
3.3 COLLECTION OF INFORMATION

Information relevant to the study’s main hypotheses was collected from several sources: students, their parents, school principals, class-teachers, school nurses and municipalities by means of structured questionnaires.

The following information is relevant to the studies included in this thesis:

3.3.1 Information at the school level

Headmasters in the sampled schools reported on selected school characteristics in the beginning of the study, including educational profile; number of teachers (in school) and students (in grades 4-6); enforced tobacco policy and actions taken to uphold the rules; anti-tobacco educational curricula. Data were obtained from all schools in the sample (n=118).

Each school in the original random sample was linked to the corresponding health care district through geographical coding by INREGIA Ltd, The Institute of Region Analysis. Information on socio-economic status (proportion of recipients receiving social benefits) in the resident population was retrieved from the registry of the Total Population Survey in 1990. This information was used to compare social characteristics between participating and non-participating schools.

3.3.2 Information from parents

Information was collected at baseline from the children’s parents, concerning their own employment, job title, education, current and past tobacco use, including use of snus and cigarettes during pregnancy with the index child. Response rate to the parents’ questionnaire at baseline was 99% (n=3,035).

3.3.3 Information from the students

Information was collected every year from 1998 to 2005, except for the first year after compulsory school, thus yielding one baseline and six follow-up surveys (Appendix 1).
The survey instrument was a self-completed questionnaire posted in the beginning of the second school semester (late January). At baseline, and during the first 4 follow-up waves, the questionnaires were completed in the classroom, sealed into an anonymous envelope and collected by the teacher. At the 2 remaining follow-up waves, the questionnaires were sent to the participants’ homes and returned by pre-paid mail. The students’ questionnaire consisted of approximately 65 questions, half of which focusing on tobacco use were kept identical at each wave. Subjects who had tried smoking or snus use (even a single puff or pinch) were asked to complete a lifetime history of use of either type of tobacco. This included, in the survey conducted the second year after compulsory school, detailed information on intensity and recency of use, as well as on symptoms of ND and withdrawal during quit attempts. Other questions, variable in extent and formulation addressed tobacco use in the social network, exposure to environmental tobacco smoke, attitudes and knowledge related to tobacco use, influence of tobacco exposure in society and school environment. The students were also asked about their psycho-social environment including major life events in the previous year, perceived academic performance, uses of alcohol, economic assets and health behaviours.

Before the baseline survey, a pilot study of the recruitment and data collection procedures was carried out in 2 schools (3 classes) in areas with high prevalence of immigrants.

Table 1 Number and proportion (%) responders in the study populations, by year and type of survey.

<table>
<thead>
<tr>
<th></th>
<th>1998 grade 5</th>
<th>1999 grade 6</th>
<th>2000 grade 7</th>
<th>2001 grade 8</th>
<th>2002 grade 9</th>
<th>2004 2 years after compulsory school</th>
<th>2005 3 years after compulsory school</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>r (%)</td>
<td>r (%)</td>
<td>r (%)</td>
<td>r (%)</td>
<td>r (%)</td>
<td>r (%)</td>
<td>r (%)</td>
<td>r (%)</td>
</tr>
<tr>
<td>Headmasters/school characteristics</td>
<td>91</td>
<td>100</td>
<td>192</td>
<td>96,9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents/family characteristics</td>
<td>3050</td>
<td>99,5</td>
<td>2768</td>
<td>92,9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Students questionnaire</td>
<td>3050</td>
<td>99,0</td>
<td>3020</td>
<td>96,2</td>
<td>3011</td>
<td>95,7</td>
<td>2976</td>
</tr>
</tbody>
</table>

n=contacted r=responders

3.4 PROCEDURE OF FOLLOW-UP

In the course of the study, tracing of the students who moved from school or changed residence address was accomplished by means of the school administration staff. After compulsory school, the National Tax Board register was also used, relying on the unique personal number (PNR) as identifier. All students were traced throughout the country. Students who emigrated were not traced, but were re-entered into follow-up if they resettled in Sweden.

At each school survey all participants received low-cost gifts such as pens, while on the 2 surveys after compulsory school early responders (within 2 weeks) were rewarded with a cinema ticket. Up to 5 attempts were made to reach non-responders, twice by ordinary mail and three times by telephone where the students were given the opportunity to complete the questionnaire by telephone interview.
3.5 SURVEY INSTRUMENTS

The questions investigating initiation and regular tobacco use as well as attitudes to tobacco were adapted from those recommended by the WHO guidelines for surveys of adolescents’ tobacco use. When no Swedish version was available translation and back-translation were made by the research team. For the assessment of ND in the second year after compulsory school selected items were used from the Modified Fagerström Tolerance Questionnaire (mFTQ), the Hooked on Nicotine Checklist (HONC) and the Diagnostic and Statistical Manual of Mental Disorders. These items were chosen based on the highest achieved response rate during a pilot study which was carried out the year before the survey (unpublished data).

All information was checked for consistency at several instances. Inconsistent reports were re-interpreted on the basis of the overall likelihood. If the inconsistency of a particular event extended through several reports, the information was discarded. The proportion of valid answers was more than acceptable in almost all cases, and for single questions ranged from 93.6% to 99.7% at baseline and from 68.6% to 99.7% at the sixth wave (2nd year after compulsory school).

3.6 DATA MANAGEMENT

The survey data was computerised and stored under protection of a password with access only to the members of the research team. In order to maintain the highest level of confidentiality, individual information was retrieved and linked together by means of a unique study code that could not lead to the identification of the subject. This code was separately linked with the PNR in an administrative database used exclusively for the tracing of the subjects at follow-up. The questionnaires were computerised by optical scanning at the Statistics Sweden (SCB). The remaining information was manually stored at the research centre. All procedures conformed to the National Data Inspection Board’s regulations aiming to prevent the violation of personal integrity in the processing of personal data. The responders were informed of these measures for protection of confidentiality which were also maintained towards third parts such as families and schools.

3.7 STUDY POPULATION

Study specific subjects and methods.

3.7.1 Schools and parents (Paper I)

a) The study samples in this paper consisted of: all schools (n=118) contacted to collaborate in the BROMS study. Of these, 91 provided collaboration (responders) while the remaining 27 were non-responders

b) parents granting their children permission to participate in the BROMS cohort study (n=3,050)

3.7.2 Mothers of the enrolled adolescents (Paper II)

The study population consisted of 2,369 (78.4%) students’ mothers who could be traced in the Swedish Medical Birth Registry and had recorded information on smoking at the first antenatal visit.
3.7.3 Sub-sample of the cohort in the 9th grade (Paper III)

The study population consisted of 583 cohort members (mean age 15 years) from a random sample of 18 schools. The final analytic sample included 520 subjects (255 boys and 265 girls) with valid questionnaire data and saliva cotinine value encompassing 89% of the original sample.

3.7.4 Tobacco users at age 17 years (Paper IV)

Of the adolescent recruited at baseline, 2,621 participated in the survey carried out during the second year after compulsory school. Of these, 819 (31.2%) reported at least monthly use of any type of tobacco at the time of the survey, and represent the analytic sample in this study.

3.7.5 All adolescents (Paper V)

Out of 3,050 adolescents with parental consent to enter the BROMS study, 3,020 5th grade students (1,537 boys and 1,483 girls), who completed the baseline assessment, represents the study base in paper V.

3.8 DEFINITION OF OUTCOMES

3.8.1 Paper I:

Main outcome in this study was the participant status at baseline (yes/no) analysed in a cross-sectional comparison of:
   a. participating and non-participating schools
   b. participating parents compared to the same-age regional or national population.

Parental time to participation, categorised as early or late response (i.e. before and after the second reminder) was also compared according to smoking status.

3.8.2 Paper II:

The aim of this study was to analyse the stability and accuracy of mothers’ recall of smoking during pregnancy as reported at the recruitment of children in the BROMS study. These 11-years’ retrospective reports of smoking status during the first trimester, categorised as non-smoking/occasional smoking/daily smoking) were compared to those recorded by the midwife during the first antenatal visit (categorised as non-smoking; <10 cigarettes/day; ≥10 cigarettes/day). This latter information was retrieved through the computerised Swedish Medical Birth Registry (MBRS) maintained by the National Board of Health and Welfare. The registry contains information from routine medical records from all antenatal clinics and delivery units. The outcome under study was total agreement, sensitivity and specificity of reports. Two analyses were conducted: first, a descriptive analysis using the MBRS as a gold standard; secondly an analysis of predictors of concordance between the 2 reports.

3.8.3 Paper III:

This study was conducted to validate self-reported cigarette and snus use among a sub-sample of 520 students in the 9th grade. Therefore, the outcome of the study was the concordance between the self-reported tobacco use in the questionnaire and saliva
cotinine concentration. Expected concordance was defined as 100% cotinine-negative among self-reported non-users and of cotinine-positive among self-reported current users. A cut-point at 5 ng/ml saliva cotinine concentration was used to discriminate current tobacco use. Self-reported tobacco use was categorised into 4 categories: not at all; monthly; weekly or daily.

3.8.4 Paper IV:

The outcome of this study was the lifetime occurrence of symptoms of ND and of withdrawal symptoms in periods of discontinued use among exclusive smokers, exclusive snus users and dual users. All variables were dichotomised into binary scoring.

3.8.5 Paper V:

The research question in this paper was whether psycho-social characteristics affect the propensity for youths to participate in longitudinal studies with long follow-up. Non-participation – the outcome of interest- was defined as a dichotomous variable, where participants were subjects who took part in all follow-up waves, while non–participants were those who failed to participate in one or more surveys after baseline. Among non-participants, subjects who declined participation all times after baseline were labelled as drop-outs.

3.9 PREDICTORS OF OUTCOME

3.9.1 Paper I:

As predictors of schools’ participation in the cohort’s recruitment, the following factors were studied: presence of an enforced tobacco policy; school size (number of teachers and students in grades 4-6); average socio-economic status in the district (proportions of recipients of social benefits in the resident population). As predictors of parents’ consent to their children’s participation, the following factors were compared with the underlying regional population: parents’ education; parents’ smoking status; maternal smoking during pregnancy; country of origin; parental cohabitation.

3.9.2 Paper II:

The mothers’ age, parity, parental cohabitation, smoking status at the time of retrospective reports, education, employment status and country of origin were studied as predictors of concordance between concurrent and retrospective reports of smoking during pregnancy. Furthermore, change of smoking behaviour between pregnancy and the time of retrospective reports was also analysed, categorised as: current non-smokers at both assessments; current smokers at both assessments; quitters and starters.

3.9.3 Paper III:

As predictors of concordance between self-reported and biologically validated tobacco use we studied the following: recency of use; intensity of use; type of tobacco used (cigarettes only or snus, alone or in combination with cigarettes); exposure to environmental tobacco smoke.
3.9.4 Paper IV:
Type of tobacco currently used (only cigarettes/only snus use/both products at least monthly) was used as predictor of lifetime reports of symptoms of ND (Appendix 2). Potential confounding factors such as gender, age at onset of tobacco use, number of quit attempts and parental education were also included in the analysis.

3.9.5 Paper V:
A number of behavioural and psycho-social characteristics were used as predictors of non-participation in this study. Apart from gender and country of origin, the following factors reported at baseline were included in the analyses: parental cohabitation, parental education, number of stressful events in the previous year and number of friends (met regularly every week) in leisure time. The following factors, assessed at different times during follow-up, were used as predictors of non-participation during the subsequent surveys: adult support (easy to confide in their parents or other adults), alcohol use, truancy and perception of school performance.

3.10 ANALYTICAL METHODS

3.10.1 Laboratory measurements
Exposure to nicotine can be measured by analyzing cotinine, a metabolite of nicotine, in blood, saliva or urine. Cotinine is a marker of tobacco use and has an in vivo half-life of approximately 20 hours, and is detectable up to 1 week after tobacco use. The level of cotinine is proportional to snus use and exposure for tobacco, and hence a valuable indicator of tobacco exposure, including second-hand (passive) smoking. In the validation study within the BROMS study, saliva was chosen as the medium for this assay. The students were asked to rinse the mouth with water (to avoid possible contamination of snus) and then chew on a role of cotton which was spat directly into a test tube. The samples were brought to the laboratory the same day, centrifuged, and stored at -80°C. Analysis was conducted by gas chromatography-mass spectrometry (GC-MS), using the method by Curvall.

3.10.2 Statistical analyses
Most statistical methods used in the analyses are common to all papers included in this thesis, and therefore presented together. Analyses specific to single papers are highlighted.
Comparisons between proportions in tabular analyses were carried out by means of the Pearson chi-square test, with statistical significance at the 5% level (p<0.05).
Logistic regression was used for dichotomous variables and results presented as adjusted odds ratios (OR) with 95% confidence intervals (95% CI). Multinomial logistic regression was used in case of categorical outcome with more than 2 categories. Potential confounders were included for adjustment in regression models and retained for final adjustment when they were significantly associated with the outcome in bi-variate analyses and modified the crude estimates by more than 10%.
Kruskall-Wallis and Kolmogorow-Smirnow tests were used for differences between medians, in cases with more than 2 categorical outcomes. In study IV factor analysis (principal factor) including an orthogonal rotation was used to identify groups of inter-related variables. Regression scoring was used to create individual scores of the factors retained by the model.
Statistical analyses were performed in

Study I and III - V: SPSS 10.0.5 for Windows (SPSS Inc. Chicago, IL, USA)
Study II, SAS version 9.1 (SAS Institute Inc, Cary, NC, USA)
Study IV Stata/SE 10.0 for Windows (StataCorp, Texas 77845 USA)
4 RESULTS

4.1 PAPER I

Of the initial random sample of 118 schools, 91 schools (77%) agreed to participate. The first level of analysis was a comparison of participating and non-participating schools. Large schools (number of teachers and students in grade 4-6 over median) and schools in higher income areas (proportion of recipients of social benefits in the resident population below median) declined participation to a greater extent. A formally (written) implemented tobacco policy was not a predictor of participation.

The second level of analysis concerns the families of the students in the participating schools. Out of 4,670 eligible students, 3,050 (65%) were supported by their parents to enter the study. Families in areas with a high share (proportion above the regional average) on welfare refused to participate to a greater extent or did not answer. The proportion of parents with college education in the BROMS cohort was about 10% higher than in the regional population of the comparable age group. Smoking was significantly more prevalent among parents who were late participants (after two reminders) compared to those who answered earlier. However, the proportion of daily smokers among all consenting parents (fathers 15%, mothers 17%) was closed to the regional average for the same age and educational group (men 17%, women 19%). This was also true for smoking during pregnancy among mothers of the subjects recruited into the cohort.

4.2 PAPER II

Reports of smoking during pregnancy obtained from 2,369 mothers at recruitment of the cohort could be matched with those recorded by the midwife when pregnant with the index child. Table 2 shows the cross-classification of smoking in pregnancy according to the 2 reports (Swedish Medical Birth Registry (MBRS) = gold standard). The sensitivity and specificity of the reports of any smoking were 84% and 93%, respectively. When smoking behaviour was dichotomised as any smoking vs. no smoking, the overall concordance was high (91%). Of the 222 discordant reports, 42 (19%) were from mothers recalling daily smoking not reported at the time of pregnancy, 93 (42%) were due to failure to recall smoking reported at the time of pregnancy, and the remaining 87 (39%) consisted of women who retrospectively reported occasional smoking in spite of being recorded as non-smokers when pregnant. Mothers who changed their smoking status during the time between pregnancy and the retrospective assessment had a lower concordance than those with stable behaviour (OR=0.2 [CI 0.2, 0.3]). Mothers older than 25 years at the index pregnancy, primiparous and highly educated women had a higher probability of agreement than younger mothers, multiparous and those with less than college education, respectively.
Table 2 Comparison between mothers’ retrospective (BROMS) and concurrent (MBRS) reports of current smoking during the 1st trimester of pregnancy, Stockholm 1998

<table>
<thead>
<tr>
<th>Retrospective reports (BROMS)</th>
<th>Concurrent reports (MBRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No smoking (%)</td>
<td>No smoking (%)</td>
</tr>
<tr>
<td>70 (%)</td>
<td>70 (n=1661)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>Smoking (%)</td>
</tr>
<tr>
<td>5 (%)</td>
<td>5 (n=129)</td>
</tr>
<tr>
<td>21 (%)</td>
<td>21 (N=486)</td>
</tr>
</tbody>
</table>

Yellow cells are concordant reports.

4.3 PAPER III

Out of the 520 students who were selected for the validation study in the 9th grade (mean age 15.0 years), 115 (22%) reported using tobacco at least monthly. The median saliva cotinine concentration was significantly different between current exclusive smokers, exclusive users of snus, and mixed users, shown in figure 7.

\[ \text{Kruskall-Wallis test for difference between medians } p<0.001 \]

*extreme value

Figure 7 Quartiles, mean and range of cotinine concentrations among current (at least monthly) users of the different tobacco products

Using a cut point for active smoking of 5 ng/ml cotinine in saliva there was a 98% concordance between self-reported non-use in the past month and cotinine concentration. Exclusive cigarette users were more likely to be classified discordantly by questionnaire and cotinine test compared to snus users (OR=3.2 [CI 1.2, 8.6]).
4.4 PAPER IV

Symptoms of nicotine dependence and withdrawal symptoms were compared between current exclusive smokers (n=466), exclusive snus users (n=209) and dual users (n=144), at the mean age of 17.6 years. Of all current tobacco users, 87% endorsed any symptom of ND. A significantly higher proportion of dual users (96.5%) reported lifetime symptoms of ND compared to exclusive cigarette smokers. Dual users reported the highest prevalence of any withdrawal symptom during periods of discontinued tobacco use, followed by smokers while exclusive snus users reported least withdrawal symptoms. In all groups, craving was the most frequent symptom reported by 65.0% of tobacco users.

4.5 PAPER V

We analysed determinants of subsequent non-participation at follow-up in the sample of 3,020 5th grade students participating at the baseline survey. During each of the follow-up surveys 1 – 5, the proportion of responders was constantly at or above 90% and declined slightly only at the last wave (Table 3).

Table 3 Responders, non-responders and dropouts in The BROMS Cohort Study 1998-2005

Most psycho-social characteristics measured at baseline were significantly associated with nonresponse any time during the study (Table 4). In logistic regression analyses adjusting for significant baseline predictors of non-participation were male gender (OR 1.5, [CI 1.3-1.8]); being born outside Sweden (OR 1.6, [CI 1.2-2.2]); parents not living together (OR 1.5, [CI 1.2-1.8]); having started smoking (OR 1.4, [CI 1.2-1.7]). Other baseline characteristics, such as change of residence, parental unemployment, peer network and prior onset of snus use were not significant predictors of nonresponse. Other characteristics measured during follow-up that significantly predicted non-participation in subsequent surveys were recent alcohol drinking (OR 1.5, [CI 1.2-1.7]) and binge drinking, ever smoking (OR 2.0, CI [1.7-2.4]) and snus use; school truancy (OR 1.5, [CI 1.2-1.9]) and perceived poor academic performance (OR 2.2, [CI 1.4-3.5]). The results were unchanged when the analysis was restricted to the 2 final waves among responders in the last grade of compulsory school.
Table 4 Behavioural and psycho-social characteristics at baseline as predictors of non-participation in any follow-up survey

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Non responder or drop-out %</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>1537</td>
<td>36.1</td>
<td>35.76</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Girls</td>
<td>1483</td>
<td>26.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2817</td>
<td>30.4</td>
<td>10.51</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>195</td>
<td>41.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother and father living together</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>2196</td>
<td>28.2</td>
<td>33.34</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>No</td>
<td>805</td>
<td>39.3</td>
<td></td>
<td></td>
</tr>
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<td>Change of residence</td>
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</tr>
<tr>
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<td>2479</td>
<td>29.5</td>
<td>19.48</td>
<td>&lt;0.000</td>
</tr>
<tr>
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<td>408</td>
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<td></td>
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<tr>
<td>Change of school</td>
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<tr>
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<td>2681</td>
<td>30.2</td>
<td>9.92</td>
<td>0.002</td>
</tr>
<tr>
<td>Yes</td>
<td>184</td>
<td>41.3</td>
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<td>Parental divorce</td>
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<td>No</td>
<td>2684</td>
<td>30.1</td>
<td>17.46</td>
<td>&lt;0.000</td>
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<tr>
<td>Yes</td>
<td>175</td>
<td>45.1</td>
<td></td>
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<td>Death of kindred</td>
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<td></td>
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<td>No</td>
<td>2117</td>
<td>30.4</td>
<td>0.74</td>
<td>0.390</td>
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<td>776</td>
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<td>Parental unemployment</td>
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<td>9.88</td>
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<td>244</td>
<td>39.8</td>
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</tr>
<tr>
<td>Number of stressful events last year*</td>
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<td></td>
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<td></td>
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<tr>
<td>0</td>
<td>1698</td>
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</tr>
<tr>
<td>1</td>
<td>878</td>
<td>33.5</td>
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<tr>
<td>&gt;1</td>
<td>390</td>
<td>39.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of friends</td>
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*Includes change of residence, change of school, parental divorce, death of kindred and parental unemployment.
5 GENERAL DISCUSSION

Longitudinal studies of tobacco uptake and use in youths have increased our understanding of the natural history, and the bio-psycho-social determinants of the transition from non-user to addicted tobacco user. The BROMS cohort study, conducted in Sweden during 1997-2005, is an exceptional endeavour in this field. The study was designed to explore the development of cigarette and snus use (Swedish smokeless tobacco) during adolescence. The studies included in this thesis focus on methodological issues necessary to elucidate and support the validity of the results obtained from this material.

Recruitment of youths from organisational units

One of the challenges of conducting cohort studies is gaining access to the target population to be recruited. Recruitment of youths from organisational units such as schools is very common. Therefore, compliance at the organisational level is as important as that at the individual level since loss of entire clusters implies a large and undesirable loss of subjects. If factors which predict non-participation at the organisation level can be identified and prevented the recruitment process will benefit. We found that large-sized schools declined participation to a greater extent as did schools in high income areas. According to previous studies, the size of a school and the relative socio-economic status of the neighbourhood where a school is located, had an impact on willingness to participate in research studies. In the BROMS study, smaller schools tended to participate to a higher degree compared with larger schools. The anticipation of high work-load for the school’s personnel in connection with the study may have impacted on participating. In this regard the size of the school may be seen as a general indicator of the complexity of decision-making at the organisation level. Another explanation may be that schools in the Stockholm region are in closer contact with universities, are often approached by researchers and procedures permitting access has to pass several layers of approval. We found a slightly higher degree of participation of schools in more deprived areas, although reports of the opposite exist in the literature. The reasons behind this discrepancy is not entirely clear, but it is possible that the aims of the research were felt as more important in areas where tobacco use was more prevalent, thus suggesting potential benefits for the students. Based on the experience from the BROMS study, it seems appropriate to suggest some key points on how to optimize the recruitment and maintenance of a school-based cohort study. First, it is important to identify a key person in each school and to involve that person early in the process. Second, it is important to underline the possible direct and indirect benefits connected to participation. In case financial reward is used, it is important to honour that formal agreement throughout the whole study. To maintain regular contacts with the school administration, and to strictly uphold the protection of the rights of the research subjects are also important cues.

Parental compliance with studies involving youths

The active parental consent sought in the BROMS study entailed a rather large drop-out of children at recruitment. Studies comparing active and passive consent strategies in research on youths demonstrated that the estimated loss of the study subjects (attributable to active consent) may be as high as 30 %. However, differences in consent rates may be observed depending on the methodology employed. For instance, in the study by McMorris, higher parental consent rates were achieved if the students had been informed in advance compared to a postal method. Based on these observations, there is no doubt that a strategy of passive parental consent would have
decreased substantially the drop-out rate at recruitment in the BROMS study. However, active parental consent was preferred owing to the long projected follow-up and the access to confidential information such as individual school health records. We found that families living in areas with a high proportion of low-income population were less likely to participate, and it can be hypothesized that the smoking prevalence in these areas is higher than average. Not surprisingly, among consenting parents the proportion with college education was higher than average but the smoking prevalence was close to what could be expected. While selective loss of under-privileged social groups follows the anticipated pattern, we cannot conclude that parental smoking influences the decision to participate because decisions taken by parents are influenced by other factors, largely independent of study-specific hypotheses or methods. In the study by Hayman, the main reason for parents declining to enrol their children was inconvenience and concern of safety.

Youths’ participation in longitudinal studies
In the BROMS Cohort Study, only 6% of the adolescents refused continued participation (permanent drop-out) during the 6-year follow-up. However, 31% were non-responders in one or more follow-up surveys. When comparing subjects who participated in all waves of data collection to those who did not we found that many psycho-social traits and behavioural factors beside tobacco use were significant and independent predictors of adolescents’ non-participation. For instance, an increasing number of stressful events, most of them connected with family disruption occurring in the previous year, were associated with non-response in a dose-response fashion. Youths reporting either the absence of close friends in leisure time or a large peer network had a higher probability of non-response, compared to the remaining group. This finding is in agreement with studies investigating internalizing-externalizing behaviours in youth that found poorer treatment retention among externalizes compared to internalizes at follow up.

Our results indicate that tobacco use at baseline is neither the only nor the strongest predictor for non-participation among youths, and that a more global profile of “social vulnerability” may predict non-response in longitudinal studies. Therefore, they offer new insights on selection processes in youth studies that may be useful for the interpretation of study results and generalization to the background population. Generalization of study findings is a complex process. Selection forces are always present in epidemiological studies. However, claiming that because of selection, valid results cannot be generalized outside the specific sample would be equal to requiring a new study for each population. Plausibility of inference to different populations can be enhanced partly by “a priori” knowledge, partly by homogeneity of findings across different subgroup in the actual sample, partly by comparing the characteristics of the study-specific population to that of the underlying population to which generalization is warranted. For instance, in the BROMS study comparisons could be made with the regional or national smoking prevalence in young populations. Among students in the second year of senior high school in the BROMS study 17% of boys and 31% of girls reported current smoking. Estimated figures at the regional level in the same year were 27% and 36% respectively.

Last, but not least our findings also suggest that baseline psycho-social characteristics of study subjects can be used to identify cues for an efficient follow-up.

Validity of youths’ reports of tobacco use
Research has supported the validity of self-reports in the assessment of cigarette smoking, both for the general youths’ population and for minorities. The concordance between reports and levels of cotinine are usually high in non users and
recent users, although limitations of the test are found among occasional users. There are few reports on validation of smokeless tobacco use in adolescence, and no study conducted in the Swedish population.\textsuperscript{113, 114} It could be hypothesized that Swedish adolescents do rather deny cigarette smoking than the use of smokeless tobacco, on the ground that it is a very frequent behaviour among Swedish men and less socially unacceptable compared to smoking, a hypothesis not verified in the BROMS study. In previous studies of school-based research, participants were informed that biochemical measures of tobacco use would be obtained. This method (bogus pipeline) has been shown to enhance the reliability of self-reports of smoking.\textsuperscript{115} However, this procedure does not constitute an assessment of validity, which was the purpose in paper III. We found that the overall validity of adolescents’ current tobacco use in the study questionnaire was very high compared with saliva cotinine. However, discrepancies between self-reports and the biological marker were common at the lower end of the consumption range, i.e. among subjects reporting occasional tobacco use. This was expected, because of the short half-life of cotinine in saliva and the varying pattern of tobacco use in this age group. Self-reported current smokers fell below the cut-off value of the biological marker more often than snus users or dual tobacco users; and therefore they were more often classified as non-users by the cotinine test. This difference may be explained through the way nicotine in tobacco is absorbed and distributed in the body. To our knowledge this comparison has not been reported before, and may have implications for the accuracy of estimate of tobacco use in adolescence by biological markers.

\textit{Validity of maternal recall of smoking during pregnancy}

Childbirth is a memorable event in a woman’s life and it is generally assumed that the memory retrieval of relevant information surrounding such major life events is accurate.\textsuperscript{97} Previous studies of recall of smoking during pregnancy indicate high stability and consistency of reports.\textsuperscript{116, 117} In a Swedish study employing biochemical validation of pregnancy smoking, 6\% of pregnant women claiming to be non-smokers had cotinine levels suggesting active smoking.\textsuperscript{118} In a context of negative attitudes to smoking, false reports due to psychological factors, such as sense of guilt may increase the propensity to conceal the habit. Important factors that affect the accuracy of maternal recall include the perceived importance of the event, how the event is defined, and the context in which the question is asked. Among the mothers of the adolescents recruited for the BROMS study, the retrospective recall of smoking during pregnancy indicated high stability and consistency. However our findings also suggest, based on lower sensitivity for daily smoking, that instrumental misclassification of smoking status may be frequent, particularly among women with decreasing and/or infrequent use, which is common in early pregnancy. Narrower categories of multiple choice answers in survey instruments are therefore advisable, in order to improve accuracy and ultimately the reliability of reports of smoking during pregnancy.

\textit{Assessment of nicotine dependence in youths}

A cigarette delivers nicotine to the brain within 10 seconds from the start of the puff, and somewhat slower in smokeless tobacco use.\textsuperscript{5} Whichever the speed of delivery, the passage of nicotine to the brain provides for strong behavioural reinforcement for tobacco use. Whether the onset of dependence and withdrawal symptoms differ in young exclusive smokers, snus users and dual users is an understudied area. Our study suggests that differences do exist, since a significantly higher proportion of dual users and exclusive snus users reported lifetime symptoms of ND compared to exclusive cigarette smokers. A slightly different picture emerged concerning withdrawal symptoms. While dual users reported the highest frequency of almost all symptoms,
exclusive snus users generally reported most symptoms to a similar or lower extent than exclusive smokers. Previous studies suggest that smokeless tobacco users are exposed to fairly high nicotine doses and that these plasma levels can be sustained for longer time than in smokers. 6, 113, 119 This presumably slower decline in nicotine plasma levels can occur due to nicotine depot effect in the mucous membrane of the mouth. 7

To gather further knowledge on the occurrence of symptoms of ND among adolescent smokers, smokeless tobacco users, and dual users the development of suitable instruments is needed. These instruments needs to assess both early symptoms of nicotine dependence, such as craving, and the topography of smokeless tobacco use, which is very different from that of smoking.
6 CONCLUSIONS

- Recruiting youths for longitudinal studies through schools may entail a substantial drop-out rate due to non-compliant schools, but this drop-out rate is probably unrelated to the study hypotheses.

- Requiring parents’ active consent to children’s participation in longitudinal studies may initially reduce the study base but increases the probability of high retention at follow-ups.

- Families living in areas with a high proportion of low-income residents are less likely to participate in tobacco research studies.

- Participation of youths in longitudinal studies of tobacco is independently predicted by several characteristics indicating social vulnerability, and not only by their tobacco use.

- There is good concordance between maternal retrospective reports of smoking during pregnancy and information reported at the time of pregnancy. The accuracy is influenced by patterns of smoking and by the sensitivity of the assessment instrument.

- Adolescents’ self-reports concerning both current smoking and current smokeless tobacco use is reliable and accurate when elicited through age-appropriate questions.

- Scales to assess nicotine dependence among adolescents should take into account frequency, intensity and type of tobacco use, since snus users and dual users experience symptoms of nicotine dependence to the same or even higher extent compared to exclusive smokers.
7 SVENSK SAMMANFATTNING


Huvudsakligt fokus för artiklarna i denna avhandling var att studera hur olika aspekter av studiens upplägg kan påverka validiteten i studien. Detta är viktig för att tolka informationen rätt och säkerställa att resultaten från studien är tillförlitliga.

Korta sammanfattningar av delarbeten I-V

Delarbete I

En analys av bortfallet vid rekryteringen av kohorten skedde på 2 nivåer. Jämförelser gjordes mellan deltagande och icke deltagande skolor och mellan föräldrar som givit samtycke till barnets deltagande och hela befolkningen. Skolor med antal elever och lärare över medianen har avstått från deltagande i större utsträckning liksom skolor belägna i välutsedda områden. Bland målsatserna som samtyckt till elevens deltagande var andelen med högskoleutbildning högre än genomsnittet i länet. I områden där andelen utlandsfödda eller socialbidragstagare var större var andelen föräldrar som tackade nej till deltagande eller inte svarade på förfrågan större än i resterande områden.

Delarbete II

En validering gjordes av 2730 mödrars retrospektiva rapportering om tobaksvanor under graviditeten med det utvalda barnet i studien. Uppgifterna jämfördes med dem som registrerats av barnmorskan enligt Medicinska födelseregistret. Samstämmigheten i rapporterna var hög (91%) vid en dikotomisk kategorisering av rökning (ja/nej). Mödramas ålder och paritet vid graviditetens tidpunkt, samt deras utbildning vid retrospektiv rapportering var signifikanta prediktorer för samstämmigheten.

Delarbete III

Detta är en tvärsnittsstudie omfattande överensstämmelsen mellan rapporterade tobaksvanor (enkät) och analys av halten kotinin i saliv (nedbrytningsprodukt av nikotin) hos 520 ungdomar (medelålder 15 år). Överensstämmelsen under den senaste månaden var 98% mätt utifrån en brytpunkt vid 5ng/ml för kotinin i saliv.

Delarbete IV

Artikeln innefattar en analys av symtom på nikotinberoende hos 466 rökare, 209 snusare och 144 blandbrukare av tobak vid en ålder av 17 år. Självskattningsskalor för nikotinberoende användes såsom frågor ur Fagerstrøms index (mFTQ), Hooked on Nicotine checklist (HONC), Diagnostic and Statistical Manual of Disorder (DSM IV). Analysen visar att snusbruk är associerat med symtom på nikotinberoende lika ofta som hos cigarettrökare, medan brukare av både snus och cigaretter rapporterade den högsta
frekvensen av symtom. "Craving" (nikotinsug) var det mest frekventa symtomet på nikotinberoende för samtliga.

**Delarbete V**

Detta delarbete är en bortfallsanalys i en studie om barns och ungdomars tobaksbruk (BROMS-tudien) omfattande 3020 ungdomar mellan 11 och 18 år. Demografiska och psykosociala faktorer studerades vid sex uppföljningstillfällen. Bortfall vid något tillfälle under uppföljningsperioden omfattade 941 (31%) ungdomar. Pojkar hade 50% större bortfall än flickor.

**Sammanfattning**

8 ACKNOWLEDGEMENTS

Health practitioners like myself are increasingly being challenged to engage in scientific training, and sometimes persuaded to proceed to conducting formal research. I embarked on a journey for which a safe arrival never was assured. I tried my best. I learned new skills, and I hope that the results may be of use in the struggle against one of the biggest health challenges of this century. I want to express my gratitude to all of you who have contributed with commitment, thoughts and experiences to this research. Especially I want to acknowledge:

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