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e-EPIDEMIOLOGY - ADAPTING EPIDEMOLOGICAL METHODS FOR THE 21ST CENTURY

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ABSTRACT

The traditional methods in epidemiological data collection are both costly and time consuming and less convenient for longitudinal large-scale studies. During the last decades, epidemiological studies suffer from low response rates, indicating a need to revise methods used in epidemiological data collection. e-epidemiology is the science underlying the usage of Information and Communication Technologies (ICT) in epidemiological studies and enable new possibilities for data collection. In this thesis four studies evaluating methods including mobile phones, the web and Interactive Voice Response (IVR) are described.

In study I, the feasibility of using an Internet-based hearing test combined with a web-based questionnaire was evaluated in a pilot study among Swedish hunters. The response rate was very low with a bias toward older individuals (40-60 years) who had access to the correct equipment at study start. Though a number of limitations, the hearing-test demonstrates a possibility of using the web in epidemiological data collection. In study II, repeated measures of physical activity level (PAL) through a Java-based questionnaire in mobile phones were compared to a gold standard of measuring energy expenditure. The Java-based physical activity questionnaire sent repeatedly through mobile phones produced average PAL estimates that agreed well with PAL reference values, indicating that the method may be a feasible and cost effective method for data collection on physical activity. Study III compared data collected through Short Message Service (SMS) to traditional telephone interviews in a population-based sample. Though the study produced very low response rate, the results on influenza vaccination status was not statistically significantly different from data collected through telephone interviews. Study IV compared data on self-reports on infectious disease where the participants could choose between web and IVR. The web was more popular than IVR and attracted more men and younger individuals with a higher completed education compared to IVR. There was no statistically significantly difference of reported infections or Influenza-Like Illness (ILI) between the two techniques after adjusting for available confounders.

Studies I, III and IV were affected by low response rates, effecting both the validity and precision of the results. All studies were affected by bias and all but study II were probably confounded by age. The mechanisms behind these factors are important to evaluate further in order to understand how it affects the collected data. However, when possible to adjust for confounders, the techniques per se did not seem to influence data negatively compared to reference data. All studies were evaluated on a Swedish population with high access to the Internet and mobile phones, and the results might not be generalizable to populations with less access. This thesis has demonstrated a fraction of the possibilities using ICT in epidemiological data collection and e-epidemiology is still in its youth. Once the techniques have been thoroughly evaluated, there are probably endless possibilities to ensure high quality data collection through methods adapted to a modern society.

LIST OF PUBLICATIONS

I. Bexelius C, Honeth L, Ekman A, Eriksson M, Sandin S, Bagger-Sjoback D, Litton J-E. Evaluation of an internet-based hearing test - comparison with established methods for detection of hearing loss. J Med Internet Res 2008;10(4):e32

II. Bexelius C, Löf M, Sandin S, Trolle Lagerros Y, Forsum E, Litton J-E. Measures of physical activity level using cell phones; evaluation against criterion methods. Manuscript submitted

III. Bexelius C, Merk H, Sandin S, Ekman A, Nyren O, Kuhlmann-Berenzon S, Linde A, Litton J-E. SMS versus telephone interviews for epidemiological data collection: feasibility study estimating influenza vaccination coverage in the Swedish population. Eur J Epidemiol 2009;24(2):73-81

IV. Bexelius C, Merk H, Sandin S, Nyren O, Kuhlmann-Berenzon S, Linde A, Litton J-E. Interactive Voice Response and web-based questionnaires for population-based infectious disease reporting. Manuscript submitted

CONTENTS

LIST OF ABBREVIATIONS

BMR	Basal metabolic rate
BMI	Body Mass Index
BP	Blood Pressure
CATI	Computer-Assisted Telephone Interviewing
CAPI	Computer-Assisted Personal Interviewing
CDC	Centre of Disease Control
CRM	Customer Relationship Management
CI	Confidence Interval
dB	Decibel
dBRefHL	dB Reference Hearing Level
dBSPL	dB Sound Pressure Level
DLW	Doubly labelled water
EISS	European Influenza Surveillance Scheme
GIS	Geographic Information System
GPRS	General Packet Radio Service
GPS	Global Positioning System
GSM	Global System for Mobile communications
HTML	Hyper Text Mark-up Language
Hz	Hertz
ICT	Information and Communication Technologies
ILI	Influenza-Like Illness
IVR	Interactive Voice Response
LISA	Longitudinal integration database for health insurance and labour market studies
MET	Metabolic Rate
NRN	National Registration Number
NTM	Scandinavian Mobile Telephone
OR	Odds Ratio
PAL	Physical Activity Level
PAQ	Physical Activity Questionnaire
PDA	Personal Digital Assistant
RR	Relative Risk
SD	Standard Deviation
SMS	Short Message Service
TEE	Total Energy Expenditure
TI	Telephone Interview
URL	Uniform Resource Locator
WAP	Wireless Application Protocol
WHO	World Health Organization
WWW	World Wide Web

1 INTRODUCTION

The development of new technologies within medical research during the last decade has led to new possibilities for researchers to assemble detailed genetic and molecular information from biological samples. Today, the technical prerequisites exist for integrating this information with demographic and lifestyle data on healthy individuals with information from administrative registers and hospital databases for large-scale prospective cohort studies. But the epidemiological methods for data collection are lagging behind as traditional methods are both expensive and time-consuming. Therefore, new and modern methods which meet the demands of both the society and the research community are needed in order to adapt the epidemiological methods to the 21^{st} century (1).

The epidemiological research has a long tradition of using self-reported data collected from population-based cohorts. Traditionally, this data has been collected through face-to-face interviews, telephone interviews and/or paper questionnaires (2), often generating high response rates and robust data. The rapid transformation of the society during the last decades has enhanced individual's possibilities for mobility, and transferring and receiving information, leading to altered possibilities for data collection in epidemiological studies. The modern society constantly generates new trends, and people change location and habits more often than twenty and even ten years ago. Daily exposure to telemarketing and surveys is considered as reasons for reduced response rates (1-4), and in the last decade the response rates in medical studies have declined considerably (5). This is especially evident among young adults (5, 6). A continuation of this negative trend can threaten the possibilities for data collection in epidemiological studies, unless we learn to understand the effects and the mechanisms behind it. By understanding potential selection forces of different methods, the methodology can be adapted in order to increase response rates and quality of collected data. This can include a mixed-mode data collection or choosing the technique according to the target population.

1.1 e-EPIDEMIOLOGY

e-epidemiology is the science underlying the acquisition, maintenance and application of epidemiological knowledge and information using Information and Communication Technologies (ICT) such as the World Wide Web (WWW), mobile phones, digital paper and Interactive Voice Response (IVR). e-epidemiology also refers to the large-scale science that will increasingly be conducted through distributed global collaborations enabled by the Internet. By using ICT in medical data collection, one can meet the high demands from a dynamic society. The new technologies also bring possibilities for enhanced data collection not possible through the traditional approaches, including real-time data collection, interactivity, tailored and personalized questionnaires and repeated measures. The advantages of using computerized methods within data collection are too good to ignore (7-9), though methods used should be highly validated in order to ensure high quality data (10). The society has already accepted and implemented ICT in daily life and there is no reason why the epidemiological science should lag behind.

2 BACKGROUND

2.1 POPULATION-BASED DATA COLLECTION

Epidemiological studies measuring the association between different lifestyle factors and outcome of disease sometimes depend on self-reports from voluntary individuals. Traditional approaches to data collection includes face-to-face interviews, telephone interviews and paper questionnaires (2). These methods are all validated and considered legitimate for complete data collection.

Interview-based methods, such as face-to-face interviews and telephone interviews have generated high response rates (once the interview subject is reached) without requiring literacy. Telephone-based interviews also ensure rapid and up-to-date data collection with quality control (11). As these methods require human resources, they are both costly and prone to bias because of sheer variability across interviewers (3). Interview-based data collection is also prone to less reliable answers for self-rating of for example diet and physical activity (11). New technologies and computerized systems were introduced in telephone interviews with Computer-Assisted Telephone Interviewing (CATI) during the 1970s and in face-to-face interviews with portable computers and Computer-Assisted Personal Interviews (CAPI) in the 1980s (2, 12). The introduction of CATI in telephone interviews increased quality of data as the computer could control input from the interviewer and more advanced questionnaires could be used. Since then, the traditional approaches have been altered and today a variety of both new collection modes and hybrids between old and new have been developed. In the 1980s IVR was developed as a computerized version of the telephone interview (13). In IVR, the respondent answers to a pre-recorded voice by pressing digits on the telephone keyboard or by answering out load. IVR will be discussed further in section 2.5.

Self-administrated methods, such as paper questionnaires and web-based questionnaires, have generally lower response rates than do interview-based methods (14), but are known to collect higher quality responds on sensitive questions and to questions known to be underreported (e.g., alcohol intake) or over reported (e.g., physical activity) (2, 15). Compared to interview-based methods, self-administrated methods are relatively cheap and not prone to be influenced by an interviewer (14). Self-administrated methods can also rely on visual communication, including illustrations, and respondents can answer the questionnaires at their own pace (16). Paper-questionnaires have been altered by computerized technologies, and following disk-by-mail questionnaires and e-mail-based questionnaires during the 1990s came web-based questionnaires which today are the most commonly used alternative to the traditional approaches (2). Though not necessarily cheaper than paper-based questionnaires, the web-based questionnaires have a number of advantages compared to the traditional approaches. Some of these are discussed further in section 2.3. The biggest concerns are still generalizability and risk of decreased response rates and coverage (7, 17, 18), especially among older individuals. The Internet has advantages beyond web-based questionnaires. One of which is to make possible objective tests which do not rely on self-reports (6). This will further be discussed in section 2.3.3.

The development of mobile devices, such as mobile phones has enhanced possibilities for data collection beyond static approaches and data can be collected in near real-time (3). Today mobile phones are a common devices in most households and people are accessible almost 24-hours a day. Though not as common in epidemiological studies, using mobile phones in different medical studies will be discussed in section 2.4.

There are additional computerized systems developed to be used in medical data collection, such as the personal digital assistant (PDA) and digital paper. However, as this thesis focuses on population-based data collection, only tools common in regular households are being described.

2.2 REACHING THE TARGET POPULATION

In order to conduct studies applicable to other populations other than the actual study population, high accessibility to all individuals is necessary. In Sweden, most individuals can still be reached through their home address. This is however not possible in all countries. In data collection through telephone interviews, most countries have relied on very high access to landline telephone numbers. Recently, more Swedish households choose to exclude their landline phones in favour of only a mobile phone (19), a trend which has also been noticed in other countries (11, 20). Figure 1 demonstrates the usage of landline phones, mobile phones and the Internet among the Swedish population in 2008 according to Statistics Sweden (http://www.scb.se). Most individuals who choose to exclude landline telephones differ in terms of socio-demographic characteristics compared to the general population, as they often are younger, wealthier individuals living in temporary households or individuals with a lower socio-economic status (21). Due to the widespread usage of mobile phones, telephone interviews depending on landline numbers might be effected by coverage bias as some populations might be excluded (22). Therefore, researchers should consider including mobile phone numbers in the sampling in order to ensure complete coverage (3, 22). This is a large challenge for telephone-based data collection, as mobile phones are individual rather than household-based, thus complicating reaching households for traditional telephone interviews (3, 11, 23). Also, the mobility of the device increases the chance for reaching individuals in transit, which might affect the nature of the response compared to established interviews in a home environment. Mobile solutions such as mobile Internet and mobile phones have also introduced new possibilities for reaching individuals in less developed countries and individuals at remote sites (24).

Though the Internet penetration today is very high in most western countries, previous studies suggest that Internet-based applications are still more applicable among specific populations, such as student or employee surveys (7, 17), while many other populations still seem to prefer mailed surveys. The characteristics of the study population have also been demonstrated to have a significant effect for the response rate in web-based studies (17). Today, the majority of the Swedish population has access to the Internet, but older age groups are still lagging behind, both regarding access but also concerning computer literacy. But these obstacles will probably be decreased, as accessibility and computer knowledge increase over time. (25).

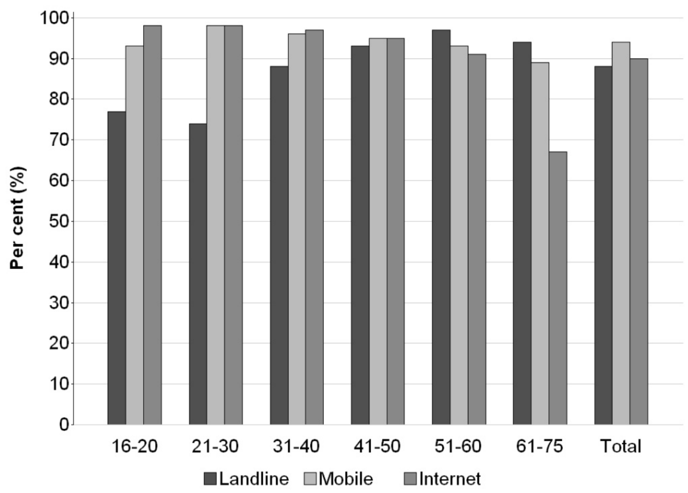

Figure 1. Usage of landline telephones, mobile phones and the Internet by age group in Sweden 2008. Source: Post och Telestyrelsen (http://www.pts.se)

2.2.1 Decreased response rates challenge epidemiological research

In recent years, response rates in surveys have been declining (5, 26-28), and in the U.S., all survey methods have seen substantial reduced response rates since the 1950s (29). Decrease in response rates threatens the generalizability of the results, as non-respondents often tend to be over-represented by specific groups, such as men, younger individuals, unmarried and individuals with lower socio-economic status which might bias the response sample (30). Many households today use answering machines and/or caller IDs to screen unwanted telephone contacts (2, 3, 11), and many households have changed patterns of when individuals are at home. The most important reason for non-participation is probably refusal once the study subject has been contacted, which also might affect response patterns (7). Higher response rates often generate less biased samples, and bias is reduced if the non-respondents reflect the same patterns in characteristics as the respondents (4). In population-based studies, it is therefore important to attract all socio-demographic groups in order to decrease the risk for biased samples. Systematically and thoroughly planned studies based on knowledge from research regarding the selection forces often decrease this risk (11).

2.3 THE INTERNET

The introduction of the Internet has significantly altered the possibilities for data collection, and using the network is often more effective compared to traditional techniques (26). Constructing a web-based questionnaire is not necessarily cheaper than a paper questionnaire, but the charges for follow-up and adding additional study subjects are considerably lower which increases the possibilities for long-term prospective studies (25). The Internet provides means for storage, organization and retrieval of large amounts of data directly linked to the questionnaire, enabling larger amounts of data and reliable statistical results (31, 32). Through cookies and automated time-stamps, all surveys conducted over the Internet can be measured in terms of response times and lurkers (individuals who enter the surveys without completion) (33). But the Internet can be extended to collect medical data through other means than web-based questionnaires, as studies enabled through patient-specific chat rooms and discussion forums (33). Using chat rooms allows interview-based data collection similar to telephone interviews.

2.3.1 Accessibility

In 2008, 84% of the Swedish population had used the Internet regularly according to Statistics Sweden (http://www.scb.se). Figure 2 demonstrates the Internet penetration among the Swedish population from 2003-2008 in the age groups 16-74 years. The corresponding access in 2008 in the European Union and the US are 61.4% and 73.1% respectively (http://www.internetworldstats.com). Though a large part of the population today has access to the Internet, the initial contact is still problematic as there are today no population-based registers with e-mail addresses (23, 34). Therefore, invitation to web-based surveys to pre-defined populations still relies on home addresses or telephone numbers. Also e-mail registers from member-based associations are often inadequate, and experience indicates at least 25% incomplete and/or misspelled addresses (unpublished data). A meta analysis by Shih and Fan (2008) including 39 papers comparing web and paper questionnaires suggests that web-based questionnaires are affected with on average 11% lower response rates than mailed paper questionnaires (17). However, the widespread penetration of the WWW increases the possibility to reach large populations through advertising on public web sites (35).

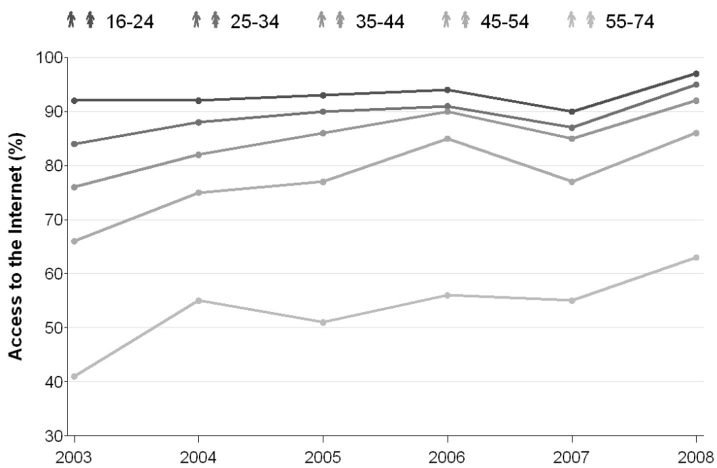

Figure 2. Regular usage of the Internet in the age groups 16-24, 25-34, 35-44, 45-54 and 55-74 between 2003-2008 Source: Statistics Sweden (www.scb.se)

2.3.2 Web-based questionnaires

Web-based questionnaires allow rapid and cost-efficient assembly of data on determinants for lifestyle and health for broad segments of the population. Web portals directly connected to the questionnaire enable instant feedback and information to the participants. They also allow animations and other web-based tools linked to the questionnaires, which can increase the interactivity and facilitate flow of information between the study participant and the study centre (8) When using a web-based questionnaire, the study subject is provided a link to a web page including the questionnaire (17). Web-based questionnaires can be divided into static or dynamic questionnaires (2). Static questionnaires are Hyper Text Mark-up Language (HTML) version of the paper-based questionnaire where the participants scroll the questionnaire and no skip patterns or other interactive tools are used. Dynamic questionnaires use the advantages of the Internet including skip-patters and error checks (16). Using web-based questionnaires in epidemiological studies has been thoroughly evaluated, and besides introducing bias in terms of highly educated individuals the method collect valid data compared to paper-based questionnaires (36).

2.3.3 The WWW – more than just a questionnaire

The Internet provides the possibility to perform large-scale screening of physical functions. By using different computerized programs, self-screening tests can indicate whether or not extensive testing is needed. They also provide an opportunity for epidemiologists to screen and collect data on physical or mental functions, such as hearing, vision or cognitive capability (37-41).

In spring 2005, a smaller pilot using a memory test was carried out among an older population (unpublished data). The study subjects (aged >60 years) were asked to download both the memory test and the support plug-in program (Shockwave) from a web page by following written instructions. The test was provided by Cogmed Cognitive Medical System AB and developed by Torkel Klingberg at Karolinska Institutet (42). The downloading of the memory test was evaluated by a small questionnaire that was linked to the web page. The questionnaire included questions regarding the web page and the logistics over the Internet. A group of around 90 participants were recruited to the pilot (66% men and 75% between 65-84 years) 97% succeeded with the log-in procedure and 75% managed to enter the memory test. Though the number of participants was low, the results from the plug-in indicate that there is knowledge of the Internet and on use of a computer, also among the elderly. It also indicates that it is possible to provide computerized animations over the Internet. More studies are needed to strength these results.

2.3.3.1 Web-based hearing test

Hearing loss is one of the most common physical impairments in the western world, and is an increasing problem among younger age groups (43). The gold standard for estimating hearing impairment is a clinical pure-tone audiogram (44), a method not suitable for large-scale population-based epidemiological studies as it demands access to equipment and trained personnel and is demanding for the participants in terms of travel to a clinic. An alternative approach for estimating hearing in epidemiological studies is self-estimation from a set of questions (45, 46), but the sensitivity of these self-estimated hearing approaches varies and the correlation to pure-tone audiogram is argued (47-52). The Internet provides the possibility to develop web-based hearing tests resembling audiograms performed at a clinic. Different devices for measuring hearing function are available online (53, 54), and different studies have been published on Internet-based hearing tests (6, 41, 55-57).

2.3.3.2 WWW and disease surveillance

Global monitoring and surveillance of influenza is dependent on various international and global systems (58, 59). Many of these systems are based on sentinel physicians and virological testing (60, 61). These are invaluable components in a complete influenza surveillance, but there is a need to supplement these mechanisms with epidemiologically stronger, population-based data collection where time-delay is shortened (62, 63). The Internet is an important component in many of the existing surveillance systems (62). Recently, different research groups have used search engines such as Google and Yahoo for monitoring influenza in the United States (64, 65). Both studies suggested that the quantity of search queries on influenza can a couple of weeks in advance predict the same pattern of seasonal influenza as according to the Centre of Disease Control (CDC). Similar results have been repeated in Canada and by a Swedish research team where search queries on national health sites were counted (66, 67). Though surveillance of search queries can become a supplement for detection of influenza outbreaks, these systems cannot provide information on socio-demographic characteristics or exact geographical information.

Web-based population-based influenza surveillance has been implemented in the Netherlands, and was in 2005 extended to Belgium and Portugal (68, 69). The system is dependent on volunteers who answer a weekly e-mail about influenza in the past week, and has a similar rise, peak and decline to the European Influenza Surveillance Scheme (EISS). The system collects socio-demographic information once the participant is registered and is probably less prone to bias from media alarms compared to search queries. But, as data is collected on a weekly basis, a more sensitive surveillance is lost. The systems also seem to exclude the oldest and the youngest age groups.

2.4 MOBILE PHONES

The mobile, or cellular, phone has been introduced to society during the last decades and is a potential tool in e-epidemiology as the device creates novel possibilities for data collection (70). In the Scandinavian countries, the Scandinavian Mobile Network (NTM) was introduced as the first generation mobile network in 1981. In Finland 1991, the first modern second generation (2G) Global System for Mobile communications (GSM) was launched, which two years later also included the SMS function. In Japan in 1999 the first mobile phone with full Internet connection was introduced, which in 2001 resulted in the first third generation (3G) mobile phone. The mobile phones are not regulated to specific sites, as computers and landline telephones, so in many cases the study subject is contacted as soon as the message is submitted, and the participants can be reached at any time inside or outside their homes (11, 71). However, an individual being in transit might decrease the risk for non-response, but also decrease the quality of the response (3, 72). Another implication in using mobile phones is the cost for the respondent, as some countries charge the mobile phone holder both for incoming and outgoing calls, including SMS, which might lead to non-response (73).

When conducting surveys using mobile phones, one should consider potential negative impact of mobile phone usage, such as risks of using the device while driving and the impact on quality of life of bystanders (74).

2.4.1 Accessibility

Mobile phones are the most widely used of the communication techniques and today more than half of the world's population has access to a mobile phone (75). In 2008, 96% of the Swedish population had access to a mobile phone (19). The access in the age group 61-75 is 89%, but is increasing every year. In 2006, 79% among Swedish children in the age group 7-14 years had access to a mobile phone, out of 58% had their own phone (76). For all age groups, using the device is more common among men than women. The accessibility increases however yearly among both women and the elderly. Worldwide, mobile phones outnumbered landline telephones in 2002 (75), and today there are more than 4 billion mobile phone subscribers worldwide (70). The dominance of mobile phones as compared to landline phones is especially evident in the developing world, which today has the largest growth of mobile accessibility (70, 75). This makes the device a potential tool for data collection where other communication tools are less available (24, 70, 77). Figure 3 demonstrates access to mobile phones in developed countries, developing countries and the entire world between 1997 and 2007 according to the International Telecommunication Unit.

One major disadvantage of using mobile phones in population-based data collection is the poor coverage of listed mobile phone numbers, thus participants have to be contacted through other mediums prior to study start (3, 78). Reasons for this include usage of pre-paid phone cards, number being listed on other individuals but the owner (e.g., a company or a relative), or the numbers not being listed. Reaching a mobile phone also depend on network connection, especially at remote sites (74).

2.4.2 Mobile phones – more than just a phone

With the introduction of the 3G mobile phones, and soon the fourth generation (4G), the mobile phone has developed from a mobile telephone to a small computer (74). The device can today hold telephone services, text messaging, Internet connection (data transfer through General Packet Radio Service - GPRS), camera, mp3 and mp4 player, etc., with data storage capacity comparable to a portal computer. This makes the mobile phone a suitable tool for both static data collection comparable to paper- or web-based questionnaires, and dynamic data collection in terms of interviews (3). The easy and almost 24-hour access to the device makes it useful when measuring variables which are varying over time, for example exercise, diet and alcohol consumption (3, 79). Compared to earlier used diaries, such as paper and web diaries, mobile phones can send reminders through for example SMS and different alarm systems.

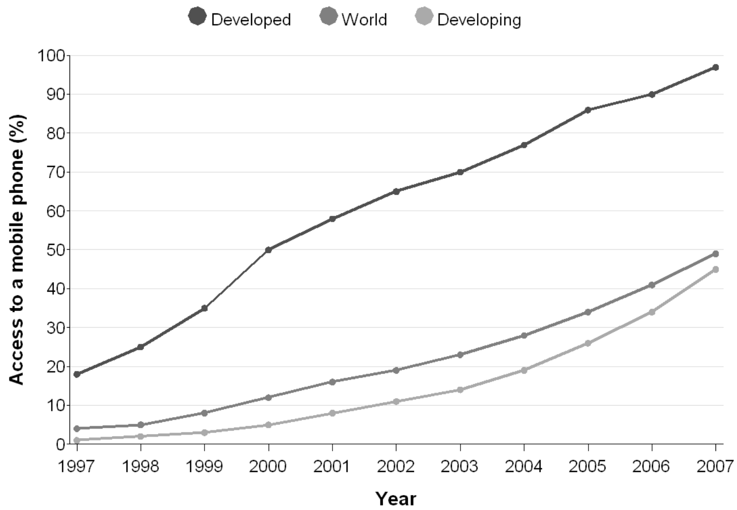

Figure 3. Access to mobile phones in developed countries, developing countries and the total world 1997-2007 Source: International Telecommunication Union (http://www.itu.int)

2.4.3 Short Message Service – SMS

SMS, or text messaging, was originally considered a paging mechanism for voice mail in the GSM network and is today one of the most frequently used modes for data transfer. The SMS function is today included in almost all mobile phones, so the technique is as accessible as the phones. Often the SMS function is limited to 160 characters per message, which makes the function useful for reminders (80) or small questionnaires with yes and no answers. SMS could also be used as a complement to ordinary questionnaires when a time stamp is required together with an answer (71). SMS has been used in the transfer of data between patient groups and health care workers in different therapy studies, such as in the self-management of diabetes (81-85) and asthma (86, 87). Also different intervention studies use the SMS function in order to motivate a behaviour change (88-90) and as patient reminders for hospital appointments (74, 91). Table 1 summarizes some therapy and intervention studies using SMS for communication between patients and study centre, and the literature has recently been reviewed by Krishna et al. (91) and Fjeldsoe et al. (92). Though most studies using SMS have been piloted on smaller populations, the acceptability among the study participants has been high and the development of these systems has paved the way for collection of medical data, also in epidemiological studies (79, 86). Contrary population-based epidemiological studies, these trials have been focused on specific patient groups. Using mobile phones and SMS as a tool for exchange of data regarding infectious diseases and adverse events between public health laboratories and central sites has been tested in both Iran and Peru (93, 94). In 2006, Bexelius et al. used SMS for a population-based collection of influenza vaccination status among the Swedish population (78). In 2008, Kuntsche and Robert used SMS in combination with a web-based questionnaire in order to collect diary data on alcohol consumptions among young adults (71), and in 2004 Anhoj et al. used SMS to collect diary data on asthma patients (86).

Though the SMS function is included in all modern mobile phones, not everyone uses the technique. In the U.S. about 30% of the mobile subscribers used the SMS function in 2007 compared to 70% in Europe (73), which limits the possibilities. Some providers of mobile phone subscriptions demand an extra subscription for the SMS functions, or the function has to be installed in the phone. Also the charge for the SMS, both sending and receiving, varies depending on country and provider. This might seriously affect response rates in SMS-based studies. However, when possible, sending an SMS as a pre-contact prior to telephone interviews has been suggested to improve response rates (73).

2.4.4 3G mobile phones and mobile Internet

The 3G mobile phones are often provided with platforms enabling media streaming, such as visual interface and sound. Sun Microsystem's programming language, Java (http://java.sun.com), is to date perhaps the most common language. Java platforms and similar platforms incorporated in the mobile phones allow all sorts of applications similar to those provided by the WWW, including shorter questionnaires (95). With the GPRS or Wireless Application Protocol (WAP) technology, data can be transferred through smaller packages and the participants only have to pay for the data transfer and not the actual time spent online. As all data can be stored in the mobile phone, the technique can be used also when there is no connection to a mobile network as data will be transferred as soon as a connection is established. As the SMS function, Java-based applications and GPRS data transmission have been used in different therapy and intervention studies, summarized in Table 2. Many intervention studies today also utilize the Internet connection by connecting different measuring devices to the mobile phones (95-98). Many of the newly developed mobile phones include the Global Positioning System (GPS), which gives the opportunity to track the geographical site of the mobile phone when the questionnaire is sent. Using GPS in mobile phones also enables monitoring of travel patterns in different populations, such as travelling patterns among adolescents in relation to risk behaviour (99) and tracking patients at emergencies (100). Compared to GPS monitors that store the data in the unit, mobile phones can transmit travelling data on an on-going basis facilitating monitoring and possibility to intervene in case of non-compliance (101). This is especially useful during monitoring and tracking infectious disease (102). Also mobile cameras have the potential for data communication in medical data transfer (90, 103).

Table 1. Intervention and therapy studies using SMS

Reference	Behaviour	Country	Sample	Study design	Findings of Intervention
Ferrer-Roca, O. 2004 (81)	Diabetes therapy	Spain	23*	Trial for diabetic management 8 month	Good satisfaction among test subjects
Ostojic, V. 2005 (87)	Asthma therapy	Croatia	8* + 8**	Randomized controlled trial 4 month	Smaller PEF variability but no difference in FEV1 compared to controls
Joo, N.-S. 2007 (88)	Obesity Intervention	South Korea	534	Anti-obesity program 3 month	Mean weight reduction of 1.5kg and mean BMI -0.6 kg/m^2 with SMS contacts
Benhamou, P.-Y. 2007 (83)	Diabetes therapy	France	15* + 15**	Randomized cross-over study 6 month	A non-significant reduction in HbA as compared to controls
Shapiro, J.R. 2008 (104)	Self-monitoring Intervention	USA	18*+ 11**	Randomized controlled trial 8 weeks	Lower attrition rate and higher adherence compared to controls
Free, C. 2009 (89)	Smoking session intervention	UK	102*** + 98*	Randomized controlled trial 6 month	Short term (4 weeks) stop smoking rate twice as high compared to controls
Patrick, K. 2009 (90)	Obesity intervention	USA	33* + 32**	Randomized controlled trial 4 month	Intervention group lost 2 kilos more than control
Kim, H.-S. 2007 (84)	Diabetes therapy	South Korea	25* + 26**	Control group Pre-test-post-test 6 month	Improvement of HbA and 2HPMG in intervention group compared to control
Yoon, K.-H. 2007 (85)	Diabetes therapy	South Korea	25 *+ 26**	Randomized controlled trial 12 month	Intervention group had lower HbA compared to control group over 12 month
Jareethum, R. 2008 (105)	Prenatal care	Thailand	32* + 29**	Randomized controlled trial 12 month	Women who received the SMS were more satisfied than control group
Franklin, V.L. 2006 (82)	Diabetes therapy among young	UK	28** + 33* + 31**	Randomized controlled trial 18 weeks	SMS together with intensive therapy improved HbA. SMS alone did not improve HbA
Hurling, R. 2007 (106)	Physical activity program	UK	47*** + 30**	Randomized controlled trial 9 weeks	Together with the Internet, the SMS increase level of physical activity compared to controls
Newton, K.H. 2009 (107)	Physical activity Diabetes Intervention	New Zeeland	38* + 40**	Randomized controlled trial 12 weeks	Combined with pedometers, the intervention group did not increase their physical activity compared to the controls
Gerber, B.S. 2009 (108)	Obesity intervention	USA	95	Feasibility study 9 month	Acceptable and feasible to use SMS in weight management program
Haug, S. 2009 (109)	Smoking session intervention	Germany	50* +64** +60***	Randomized controlled trial 3 month	SMS-based interventions are attractive for young adults. No differences to controls.

* SMS **Control *** SMS and additional technique

Table 2. Intervention and therapy studies using mobile phone with Internet connections

Reference	Behaviour	Country	Sample	Intervention Technology	Study design	Findings
Kollmann, A. 2007 (110)	Diabetes Therapy	Austria	10	Java-based software in mobile phone and web portal	Feasibility study 3 month	Technique was valid and well accepted
Farmer, A. 2005 (95)	Diabetes therapy	UK	-	Java-based program in mobile phone Glucose meter	-	Technical report
Scherr, D. 2006 (96)	Cardiac patients therapy	Austria	20	Mobile phone with WAP connection, BP monitor	Feasibility study 90 days	Technique reliable and easy to handle
Morak, J. 2008 (111)	Obesity Therapy	Austria	25	Mobile phone with Internet connection	Feasibility study 70 days	Benefit of system dependent of willingness to participate
Hareva, D.H. 2009 (112)	Supportive Interventions	Japan	5	Mobile with Internet connection e-mail contacts and web page	Feasibility study	System support patients in self-management
Logan, A.G. 2007 (97)	Diabetes therapy and hypertension	Canada	33	Bluetooth enabled BP monitor, Mobile phone with GPRS connection	Feasibility study 4 month	Patients decreased ambulatory PB and improved BP control
Cho, J.-H. 2009 (98)	Diabetes therapy	South Korea	38* + 37**	Glucometer connected to mobile phone or Internet-based therapy	Randomized controlled trial 3 months	Mobile phone group is as efficient as the Internet-based therapy to decrease HbA.

* Mobile phone group ** Internet group

Real-time data collection on physical activity enabled through Java and Internet connection in mobile phones

Physical activity is thought to play an important role in the etiology of many diseases including cardiovascular diseases, diabetes, colon cancer and breast cancer (113, 114). But to further understand the preventive effects of physical activity, more epidemiological studies with solid data collection are needed. For practical reasons, many studies estimate physical activity using self-reports through questionnaires, which are easy to use, non-invasive and suitable for large-scale studies (115-121). But retrospective recalls of physical activity are limited since they are based on memory and prone to misclassification due to reporting bias (122). A systematic review by Nielsen et al. in 2008 analyzed 20 papers comparing 36 Physical Activity Questionnaires (PAQ) with the gold standard Doubly Labelled Water (DLW) (123). The article concluded that the validity of PAQ's is not sufficient compared to DLW. Physical activity records, in which the participants enter their level of physical activity throughout the day in a diary, have been argued to be a more accurate measurement (124, 125). This method is sensitive to compliance and demanding for both the study participants and the study centre as numerous data entries are recorded and analyzed (126). There are other, more objective methods to assess physical activity, for instance heart rate monitors and accelerometers, but these methods are also demanding in terms of processing large data quantities before a reliable variable can be derived (127). A number of studies of Internet-based physical activity interventions have been published (128), but for diary data the Internet has the same limitations as paper-based methods. Mobile phones are a time and cost effective medium for collection of diary data (71), and could be used for real-time measures of physical activity. By using the SMS function for reminders, Java-based programs and the mobile Internet connection, the compliance could be increased and reporting bias reduced.

2.5 INTERACTIVE VOICE RESPONSE – IVR

IVR via landlines or mobile phones is a useful tool for data collection for shorter questionnaires and/or self-reported data. The advantages as compared to regular telephone interviews are decreased costs and decreased risk for bias due to the interviewer, given high quality of the recorded voice (13). However, in comparison, IVR-based interviews are more affected by drop-outs and non-response (129). Compared to telephone interviews, IVR is often limited to shorter questions with short answers. In surveys outside the medical area, IVR has been used among highly motivated participants, e.g., employee and customer satisfaction surveys (26). As IVR can be used from both landline and mobile phones, IVR has an almost 100% accessibility, including hard-to-reach groups (13). As SMS, using the technique in mobile phones ensures an almost real-time measurement (130). IVR has been used in medical research since 1989, and has since been used in a number of studies, including prevention and intervention studies (130, 131) and diagnosis and management of chronic disease (132). The high accessibility and the easy-to-use technology make the device especially useful among individuals with less knowledge of more modern techniques, such as the elderly. IVR has previously been used in a surveillance system for influenza among the Swedish population.

2.6 MIXED-MODE INCREASES RESPONSE RATES

A mixed-mode data collection is used both to reduce costs and to increase response rates (16, 133). Often, researchers begin the data collection with a cost effective mode and add a more expensive mode to follow-up non-respondents and to compensate for the weakness of the primary method (134). The possibility of different modes in data collection is an opportunity to tailor the data collection mode to the specific study population (133, 135). Web-based modes might be more suitable for a younger population, and traditional approaches might be kept among elderly (26). When contacting a population-based sample through telephone interviews, a mixed-mode with both landline phone numbers and mobile phone numbers might be preferable (21), and in self-administrated surveys using the WWW, paper-based questionnaires should be included as a complement (25). For large population-based studies including all age groups, a mixed-mode with the choice of two or three techniques could therefore be an alternative. However, one should be careful when introducing an alternative method as the different modes might have different conditions of phrasing the questions or respond categorizes, which might affect the response (26, 134). Audible expressions from interview-based techniques might for example effect the response patterns differently from visual expressions in self-administrated methods (133).

3 AIMS

The aim of this thesis is to further develop and evaluate Communication and Information Techniques in order to establish e-epidemiology as an efficient tool for collection of epidemiological data

Specific aims:

- To evaluate an Internet-based hearing test

- To evaluate the feasibility and validity of measuring Physical Activity Level (PAL) through a Java-based questionnaire in mobile phones

- To evaluate the use of SMS via mobile phones as a tool for data collection in epidemiological studies

- To evaluate a web-based questionnaire and IVR as tools for self-initiated lay reporting of upper respiratory tract infections, including influenza-like illness (ILI)

4 SUBJECTS AND METHODS

4.1 REGISTRY RESOURCES AND NATIONAL REGISTRATION NUMBERS

Compared to many other countries, the Scandinavian countries have a long tradition of population-based registers. These registers include the Cancer Registry, Death Registry and In-patient Registry in the National Board of Welfare. But also registers at Statistics Sweden including the Population Registry. The registers enhance the possibilities to reach predefined groups of the population with explicit characteristics and population-based sampling randomized by socio-demographics can be carried out and data can be obtained for both respondents and non-respondents; a major advantage compared to other countries (136). In 1947, all Swedish residents were provided with a unique 9 digit National Registration Number (NRN). In 1967, the number was extended with an extra digit and today the NRN consist of six numbers indicating date and year of birth, a three-digit serial number and a control number (137). The uniqueness of the NRN's gives a possibility for record linkage between the different registers, but also linkage to collected data in order to provide information on disease and socio-demographic information. The registers used in this thesis are listed below.

The Swedish register of population and population changes
The Swedish register of population and population changes contains Swedish census data since 1960. The register includes the current home address and NRN of each Swedish resident from the end of each year. Since 1969, the register also includes information on emigration.

Longitudinal integration database for health insurance and labour market studies (LISA)
LISA was released in 2004 and the register is collaboration between Statistics Sweden, the Social Insurance Agency and the Swedish Agency for Innovative Systems. The register includes annual data from 1990 on all individuals from 16 years and older. The register today contains information from the labour market and educational and social sectors (http://www.scb.se).

The Swedish registry of education
The Swedish registry of education was first constructed in 1985 and is based on the 1970/1990 census. Since 1985 it has been updated annually with data on individuals 16-74 years old who are registered as resident of Sweden at January 1 annually. The register contains a core of demographic and education data (http://www.scb.se).

The Swedish National patient registry
Since 1987, the Swedish national patient registry (Inpatient registers) holds information on all completed hospitalization occasions. The register includes information about main and second diagnoses and surgical procedures (ICD 7 and 8 codes), preventive care, external cause of injuries and poisoning, NRN, gender, age, and home address (http://www.sos.se).

4.2 STUDY DESIGN

4.2.1 Study I

The aim of the pilot-study was to evaluate the feasibility of using an Internet-based hearing test in a cohort of Swedish hunters. The hearing test was evaluated in terms of comparison to a self-estimated question (Figure 4). The study was also evaluated in terms of the feasibility of combining a web-based questionnaire and an Internet-based hearing test for data collection in a cohort of Swedish hunters.

How is your hearing?

◉ good ◉ minor hearing loss ◉ moderate hearing loss ◉ severe hearing loss

Figure 4. The self-estimated hearing question used in the comparison against the results in the hearing test.

In March 2007, 560 (500 men) members of the Swedish Hunters' Association aged 20-60 years were contacted through a mailed invitation letter. Subjects were selected proportionally to the distribution among the members in terms of gender and age. The mailed invitation included a description of the study and a personal login and password to the study web site (https://jagarhorsel.ki.se). After the initial invitation, two paper reminders were sent, followed by a telephone reminder. Reminders were sent to subjects who had not yet completed the questionnaire and the hearing test without declining participation, and to those who had answered the questionnaire but not completed the hearing test.

The study flow-chart is presented in Figure 5**.** The study web site, including a web-based questionnaire and an Internet-based hearing test, and was assessed through a personal username and password. Each participant completed the questionnaires before he/she could access the hearing test. The web-based questionnaire included questions regarding background, hunting-specific questions, self-estimated hearing, occupation and military service, problems with hearing, medications and spare-time activities. The hearing test was based on Java 5.0. If the participant did not have the correct version of Java in his/her computers, the program could be downloaded free of charge. Before the participant could start the hearing test, the sound levels were calibrated against a reference person to compensate for variations in different headphones and noise interference from the computer and the surroundings. Prior to the calibration of the test, the participant was instructed on how to set the correct volume level on the computer and how to use the headphones.

The reference person was presented with a volume slider having a fine-tuned scale ranging over 30 dB. He or she was then instructed to move the slide head to a barely audible position (RefHL for the frequency), and then request the program to present the next tone. The tone was a frequency-modulated sinus tone; a slightly vibrating tone which can be heard on headphones having "dead points" on certain pure frequencies. This tone was presented to both ears to get the lowest hearing threshold on each ear. The procedure started from 500 Hz and was repeated for

1000 Hz, 2000 Hz, 4000 Hz, 6000 Hz and 8000 Hz. Quality check of the calibration of the RefHL data was performed on the finalized data.

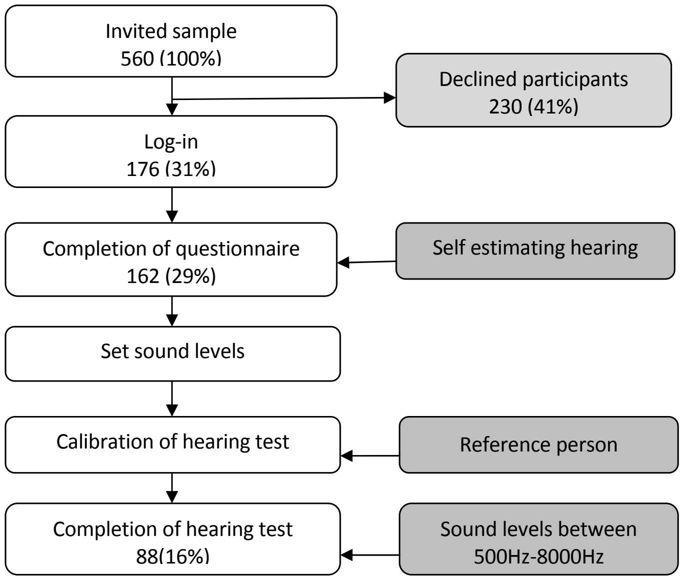

Figure 5. Flow-chart of a pilot study evaluating an Internet-based hearing test and web-based questionnaire

During the hearing test, intensity levels were presented between 0 (from reference calibration) and 60 dB sound pressure level (dBSPL). The participant pressed the space bar on the computer keyboard to register that a tone was heard. When a tone was registered as heard, the test presented the same frequency at a 6 dB lower intensity level. When a tone was not heard the test instead presents a tone of 6 dB higher intensity level. The test proceeded for both left and right ears to settle the hearing levels for each frequency. This test procedure was a web adaptation of established clinical audiometric testing and follows the guidelines for clinical audiometric testing (138).

The audiometric data from the hearing test was classified according to the definition by World Health Organization (WHO) (Table 3) for normal hearing, minor hearing loss, moderate hearing loss, and severe hearing loss (139).

Table 3. Definition of cut-off levels for hearing capacity

Hearing capacity	**Cut-off level for hearing capacity**
1. Normal hearing	0-25 db on all frequencies
2. Minor hearing loss	26-40 db on one or more frequencies
3. Moderate hearing loss	41-60 db on one or more frequencies
4. Major hearing loss	>60 db on one or more frequencies

The result of the hearing test was compared to the self-estimated hearing question from the questionnaire (graded according to the same scale). The analysis was based on the audiometric data from the best ear in the hearing test.

4.2.2 Study II

Energy expenditure in response to physical activity can be obtained as total energy expenditure (TEE) divided by basal metabolic rate (BMR) giving physical activity level (PAL). In free-living subjects, PAL can be calculated from measurements of TEE obtained using the DLW method and measurements of BMR assessed using indirect calorimetry (126, 127, 140), which in this study was measured in the morning of the first study-day. The aim of the study was to evaluate data on PAL collected daily during fourteen days through a Java-based questionnaire in mobile phones against the PAL obtained through DLW and indirect calorimetry. The measuring technique was also compared to two prior validated questions on physical activity.

In this study, 22 healthy women were recruited to a study on energy metabolism and physical activity. Each woman was given a dose of stable isotopes (0.09 g $^2H_20$ and 0.23 g $H_2{}^{18}0$ per kg body weight) and asked to collect urine samples during the subsequent 14-day period, giving a reference PAL (PAL_{ref}). The isotopes are distributed evenly over the body and secreted through urine depending on level of physical activity. The rate of which isotopes are eliminated from the body is proportional to the degree of metabolic carbon dioxide production, and the TEE over the study period can be calculated. Before the study period, each woman downloaded the Java-based questionnaire in her mobile phone. If the mobile phone didn't support the Java script, it was possible to borrow an appropriate phone from the study centre. During two weeks, each woman received an SMS each day at 9 pm as a reminder to answer two questions about her physical activity during the same day through the Java-based program on her mobile phone (Table 4). All data were delivered to the study centre in real-time through the mobile phones GPRS connection. The study centre could contact the women through SMS throughout the study. The last day, the women delivered the urine samples and answered two paper questionnaires regarding physical activity during the preceding 14-day period.

Table 4. Two questions asked using mobile phones in order to measure physical activity level (PAL)

1. How physically active have you been during work/daytime today?	
Answer	PAL (141)
a. Mostly sitting	1.55
b. Sitting/standing/walking	1.65
c. Standing/walking most of the time	1.85
d. Heavy work	2.2
2. How physically active have you been during leisure time/evening today?	
Answer	Additional contribution to PAL (142)
a. Mostly sitting	+0
b. Light/walking 30min	+0.06
c. Moderate/cycling≥30min	+0.15
d. Sport/cycling≥60min	+0.29

Calculation of PAL from mobile phones

The two questions were converted to PAL as shown in Table 4. The questions cover both physical activities during day/working time and evening/leisure time. Daily PAL was calculated through summarizing the answers from the two questions. The questions have not been used elsewhere, but similar questions have been used in other studies (143, 144). The PAL values for the first question were derived from Black et al. (141) and PAL for question 2 was derived from Ainsworth et al. (142). The mean of the 14 PAL values from day 1 to day 14 was referred to as PAL_{mobile}.

Calculation of PAL from the two paper questionnaires

The first questionnaire has been used in previous epidemiological studies and consists of one simple question (145, 146) where the woman grades her physical activity during the last two weeks between 1 (low) and 10 (high). The woman was informed on how to answer the question and the answer was converted to PAL_{quest1}, where value 1 represented a PAL-value of 1.3. Every step up to 10 represented a 0.1 increase in PAL up to 2.2. In the second questionnaire, the women reported physical activity during one average 24-hour period during the last two weeks (116) by reporting the number of hours and minutes spent in nine different activity categories with assigned MET (Metabolic Energy Turnover) values (145). PAL_{quest2} was calculated as the sum (MET x number of minutes for each activity category) divided by 1440 minutes.

4.2.3 Study III

The study aimed at evaluating the feasibility of collecting influenza vaccination status among the Swedish population through SMS in mobile phones. The collected data was evaluated against traditional telephone interviews.

In total, 4,550 individuals in the age group 0 to 100 years were randomly drawn from the population register at Statistics Sweden and allocated into two groups: 2,400 in the SMS group and 2,150 in the telephone interview group (TI group). Telephone numbers were extracted through record linkage from the most complete telephone directory in Sweden (147). If more than one phone number was listed in either the SMS group or the TI group, one number was chosen randomly. In the TI group, a landline number was primarily used and a mobile number if no landline number was found. If only a number to a partner to the selected individual was found (primarily landline or secondary mobile), this number was used. If either a mobile phone number (SMS group) or any number (TI group) was found the participant was contacted through an invitation via regular mail. Children under 16 years were contacted via their parents, and individuals who were unable to handle the technique were encouraged to delegate the task to someone else. Individuals who did not decline participation were contacted and asked three questions including the question “Have you been vaccinated against influenza since October 2005?”, either through an SMS or a telephone call in March 2006. Attrition and study flow are shown in Figure 6**.**

The SMS group received the first SMS at 5 pm on a weekday and answered by texting 1 for “yes”, 2 for “no”, 8 for “don’t know” or 9 for “abort session”. If the participant asked to end the session, no further contacts were made. Reminders (the same message) were sent to the non-respondents the following day and yet again one week later. Simultaneously, attempts were made to contact individuals in the TI group between 5 pm and 8.30 pm during five consecutive weekdays.

All collected data was linked to the LISA register at Statistics Sweden. Information was obtained about age and gender, marital status, size of household and family income, highest degree of education and occupation (categorised according to the Swedish Standard Classification of Occupations 1996 (148). The data file was further linked to the Inpatient register at the National Board of Health and Welfare in order to get information about hospitalizations between 1999 and 2004.

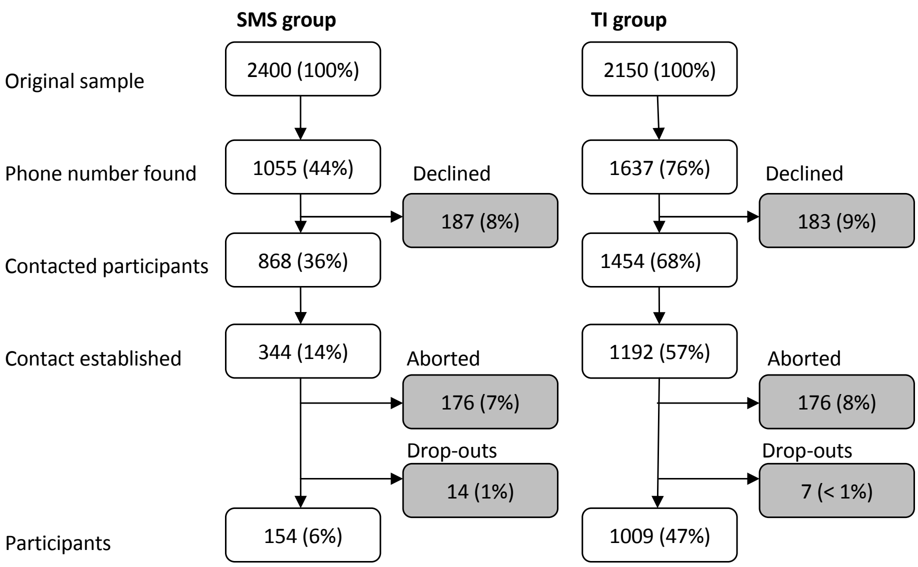

Figure 6. Study flow and attrition for the SMS group and the TI group respectively

4.2.4 Study IV

In study IV, IVR and a web-based questionnaire were used in order to establish a population-based surveillance system for detection of annual influenza epidemics. The aim of the study was to investigate the degree to which the reporting method *per se* might influence incoming self-reports by comparing participants who initially chose the web with those who chose to use IVR. Of interest were possible socio-demographic selection forces and proportions of registered participants reporting infections.

A random sample of 14,000 Stockholm county residents, aged 0 to 95 years, was drawn from the Swedish population register at Statistics Sweden and invited to participate through a mailed invitation. For children under the age of 16 years, the parents were contacted as proxy reporters in lieu of the child and elderly with impediments could ask a deputy to act as a substitute. Participants were required to first register for the study by entering their NRNs at the study web site or via IVR. The participants' choices of technology for this initial registration were used to categorize them as belonging to either the web group or the IVR group.

Registered participants were asked to report all new occurrences of upper respiratory tract infection (influenza-like illness [ILI] or "common cold") between October 2007 and May 2008 by answering a short questionnaire about specified symptoms and time since onset. All participants could alternate between the two contact modes throughout the follow-up period. Both the website and the IVR platform presented the same branched set of questions and were connected to the same database. Reminders were sent to all registered participants at Christmas (study week 12) and around Easter (study week 25). At the end of the study, all individuals included in the total sample received a final questionnaire including questions about registration and influenza vaccination.

After data collection was completed, a dataset including all registered participants was linked to the LISA register at Statistics Sweden to obtain demographic information on each individual. Variables used in the analysis were gender, year and month of birth, marital status, highest completed education, household size and total household income. For children under the age of 18, parental data was received on highest completed education, occupation and marital status. Corresponding data (excluding parental data) on the total sample was received on an aggregated level. To evaluate differences between reporting patterns over the study period and techniques, reports were separated into reports of any infection and reports of ILI (ILI – i.e., a symptom pattern conforming to the case definition proposed by the European Centre for Infectious Disease Control [http://ecdc.europa.eu]). As some participants reported symptoms on more than one occasion, only the first individual report was used. Week by week, the proportions of individuals reporting occurrence of a new infection out of all participants was estimated in the web and IVR groups respectively and plotted in visual graphs for comparison.

4.3 STATISTICAL METHODS

All four studies have been evaluated mainly in terms of descriptive statistics. In study I, the Pearson chi^2 test was used in order to compare the distribution of socio-demographic variables between full respondents and questionnaire respondents. In study III, the distribution of socio-demographic characteristics among respondents, contacted sample and total sample was described by visual graphs and in study IV, data on a continuous or ordered categorical scale were compared with the Wilcoxon's rank-sum test while data on a nominal scale were compared by Pearson chi^2 tests. All statistical tests were done using SAS 9.1.3 software.

Study I: Kappa coefficient
In study I, the kappa coefficient was used in order to measure the agreement between the self-estimated hearing question and the results from the hearing test. The kappa measures agreement in contingency tables by comparing the proportion of the data scored equal that is the data found in the table diagonal, with what is expected from chance alone. (149). For perfect agreement the kappa takes the value 1 while a value

≤ 0 is obtained when there is no agreement. The major disadvantage of the kappa is that there is no single widely accepted cut-off for agreement.

Study II: Bland and Altman plot

Bland and Altman published their first paper on how to assess agreement between two measuring techniques in 1986 (150). The method is developed in order to compare a new technique against an already established. Other measurements, such as correlation coefficient (*r*), do not necessary mean that the agreement between two techniques is high, even though the correlation is close to one. Correlation measures the strength between two variables. A high correlation between two variables will accrue if there is a strong linear relationship between the two techniques regardless of the techniques measures equal. Bland and Altman suggested plotting the difference between two methods against the mean of the two methods. This will give information on not only the agreement, but also the relationship between the measurement error and the true error. Using the mean is one of the main advantages in the Bland and Altman plot, as using the difference is by definition correlated with any single technique. Also, as the true value is not known, the mean of the two measurements is the closest estimation. The interval of 2SD from the mean of the two methods is referred to as the limits of agreement.

In study II, the Bland and Altman procedure was used to calculate the agreement between PAL_{mobile}, PAL_{quest1} and PAL_{quest2} versus PAL_{ref} To test for trend within methods, a linear regression model was fitted between (x) and (y). Intra-class correlation was used to measure intra individual variation of daily physical activity levels through mobile phones. All statistical tests were done on the two-sided 5% level of significance.

Study III: Multiple logistic regression

The multiple logistic regression models is in epidemiological research used to calculate the probability of occurrence of an event as a function of one or several dependent variables (151, 152), thus controlling for confounding factors. By calculating the ratio between two probabilities, the odds ratio (OR) for an exposure adjusted for all other variables is obtained (153). The logistic regression model is a generalized linear model on the binomial scale using the *logit* transformation. The function of the model is:

$$\text{logit}(p) = \ln \frac{p}{1-p} = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k$$

In this thesis, the multiple logistic regression models were used in paper III. As no data was available on parents of children, data was sparse and a log-binomial regression model did not fit the data. In the first model, being vaccinated against influenza was the dependent variable. The analyses started with a model that only included the two groups (SMS or TI), and then stepwise introduced available background variables (age, gender, education and family size), where data was complete for all participants to explain observed dissimilarities in vaccination coverage between the two groups. As influenza vaccination among the youngest age group (0-17 years) was very rare, the two youngest age categories were merged into 0-39 years. In order to measure the effect of the different techniques on willingness to participate, the second model was fitted with non-participation (yes/no) as the dependent variable. Also in this model, the analyses started with a model that only includes the two allocation groups, and then available background variables (age, gender, education, family size and family income) were step-wise introduced with in order to adjust for potential confounding. As data on education was missing in the youngest age group (0-17 years) this age group was excluded from the analysis. Also other observations including missing data were excluded from the analysis. Group differences for all regression models were expressed in terms of OR. All statistical tests were done on the two-sided 5% level of significance. The goodness of fit of the fitted models was evaluated by using the model deviance. Likelihood ratio tests were used in the logistic regression models to evaluate the addition of a variable.

Study IV: Log-binomial regression

In study IV, a log-binomial regression model was used in order to estimate the relative risk (RR) of reporting an infection and/or ILI. The log-binomial regression model is a generalized linear model used for calculation of dichotomous outcome with binomial distribution of error (154). In the log-binomial regression model, the *log* function is used. The model produces an unbiased estimate of the adjusted RR. The function of the model is:

$$\log(p) = \beta_0 + \beta_1 X_1 + \dots + \beta_k X_k$$

In study IV, the log-binomial regression models were fitted to assess the effects of choice of reporting technology and other measured background factors on the risk of reporting at least one infection. First, crude RR of ever reporting an infection (yes/no) during the follow-up period was fitted for the web group, relative to the IVR group. The model was then adjusted for age group, gender, level of education, household size and family income. As in study III, marital status was highly correlated with size of household, and not included in the regression models. For children under the age of 18, socio-economic data on their parents were obtained in the regression models (Table 3 and 4). The goodness of fit of the models was evaluated by using the model deviance. Likelihood ratio tests were used to assess the relative importance of the model covariates. All statistical tests were done on the two-sided 5% level of significance.

4.4 ETHICAL CONSIDERATIONS

The regional ethical committees in Stockholm have approved all four studies. Also all studies have followed the Personal Data Act on computerized registration of personal data. Sensitive data has not been collected in any of the studies. In study II, a written informed consent was collected from all participants. In studies I, III and IV, agreement to participate in the study was considered informed consent. All invited participants had the option to terminate participation throughout the studies and withdraw all individual data. All data was stored on servers protected by double firewalls and was only assessed by the study group.

5 RESULTS

5.1 STUDY I

Attrition and socio-demographic distribution

Attrition and study flow are demonstrated in Figure 5. After three reminders, 74 out of 560 (13%) completed the questionnaire only (questionnaire respondents) and 88 (16%) completed both the questionnaire and the hearing test (full respondents). 230 (41%) declined participation and 158 (28%) were never reached (non-respondents). The distribution of gender was similar in all groups (Table 5). The full respondents were older than the non-respondents and the questionnaire respondents. The full respondents were not statistically significantly different from the questionnaire respondents in terms of socio-demographic characteristics or self-estimated hearing prior to the test (Table 6). When looking at access to the necessary equipment, full respondents were more likely to have headphones at home (p=0.003) and the correct Java version in their computers (p=0.007) compared to questionnaire respondents. Reasons for declining participation were lack of time, lack of interest in the study, lack of headphones, having no experience of gun-shots or hunting, or already having a hearing loss and therefore considering themselves not the correct target for the study.

Table 5. Distribution of age and gender among total sample in a pilot study for evaluating an Internet-based hearing test among 560 members of the Swedish Hunters' Association

	Non respondents n=154 (28%)	**Declined study n=230 (41%)**	**Drop outs/ Lurkers* n=14 (3%)**	**Questionnaire respondents n=74 (13%)**	**Full Respondents n=88 (16%)**	**Total n=560 (100%)**
Gender						
Men	138 (28%)	200 (40%)	13 (3%)	68 (14%)	81 (16%)	500 (100%)
Women	16 (3%)	30 (50%)	1 (2%)	6 (10%)	7 (12%)	60 (100%)
Age category						
20-34	51 (35%)	57 (39%)	3 (2%)	17 (12%)	17 (12%)	145 (100%)
35-49	63 (25%)	110 (43%)	7 (3%)	35 (14%)	39 (17%)	254 (100%)
50-60	40 (25%)	63 (39%)	4 (2%)	22 (14%)	32 (20%)	161 (100%)

*Individuals who entered their password on the study web page without completing the questionnaire.

Hearing test

In total 126 hearing tests were carried out by 88 participants. Among the duplicates, the test with the smallest degree of hearing loss was used in the analysis. After removal of those hearing tests with an incorrect reference, 61 hearing tests remained. Mean age was 45 years. Thirty two out of 61 (52%) reported hearing loss in the self-estimated hearing question and 12 (20%) had hearing loss according to the Internet-based hearing test. This was statistically significantly different (p<0.001). Among those who had a hearing impairment according to the Internet-based hearing test, six (50%) had classified their hearing differently in the self-estimated question. After excluding severe hearing loss, the simple kappa coefficient was calculated to 0.18 (95% confidence interval 0.005-0.359), indicating a slight agreement between the two measurements. Only one of the 61 individuals who had performed the hearing test had a documented ear injury.

Table 6. Socio-demographic characteristics among questionnaire respondents and full respondents in a pilot study for evaluating an Internet-based hearing test among 560 members of the Swedish Hunters' Association

	Questionnaire respondents n=74 (%)	Full respondents n=88 (%)	p-value
Gender			
Men	68 (92%)	81 (92%)	0.97
Women	6 (8%)	7 (8%)	
Age category			
20-34	17 (23%)	17 (19%)	0.65
35-49	35 (47%)	39 (44%)	
50-60	22 (30%)	32 (36%)	
Household			
1	12 (16%)	6 (7%)	0.16
2	26 (35%)	27 (31%)	
3-4	31 (42%)	43 (54%)	
5-6	5 (7%)	11 (69%)	
Missing		1 (1%)	
Education			
Preschool	9 (12%)	9 (10%)	0.80
High School	30 (41%)	34 (39%)	
College/University	35 (47%)	43 (49%)	
Missing		2 (2%)	
Environment			
Large city	10 (13%)	8 (10%)	0.64
Suburb	11 (15%)	9 (10%)	
Medium-sized city	10 (14%)	14 (16%)	
Small town	14 (19%)	23 (26%)	
Countryside	29 (39%)	33 (38%)	
Missing		1 (1%)	
Java			
Yes	23 (31%)	44 (50%)	0.007
No	51 (69%)	40 (45%)	
Missing		4 (5%)	
Reported email			
Yes	73 (99%)	86 (98%)	0.66
No	1 (1%)	2 (3%)	
Headphones*			
Yes	48 (39%)	74 (60%)	0.003
No	26 (61%)	13 (30%)	
Missing		1 (1%)	
Self-estimated hearing			
No loss	44 (59%)	39 (44%)	0.06
Minor loss	18 (24%)	35 (40%)	
Moderate loss	8 (24%)	12 (14%)	
Severe loss	4 (5%)	1 (1%)	
Missing		1 (1%)	

*Have headphones at home prior test

5.2 STUDY II

Compliance and characteristics of study participants

Out of the 22 women, 14 (64%) had a mobile phone that supported the Java-based program and during the two-week study period, all but two women answered all the daily questions. These two women missed a reporting occasion at one and two times respectively. None of the women asked to terminate the reporting before the end of the 14-day period. The women's mean age was 35.1±8.3SD. Four were overweight (Body Mass Index [BMI]>25) and two obese (BMI>30). At baseline, ten (45%) women reported that they never exercised or that they exercised 1-2 times per week, while twelve women (55%) reported that they exercised at least three times a week.

PAL assessed using mobile phones

Figure 7 demonstrates the Bland and Altman plot for the PAL_{mobile} compared to PAL_{ref}. The average PAL_{mobile} was 1.82 compared to 1.83 for PAL_{ref}, These values were not statistically significantly different. The mean difference for PAL_{mobile} and PAL_{ref} was 0.014 with limits of agreement of 0.29. The test for trend was not statistically significant (slope of regression line=-0.58; p=0.08).

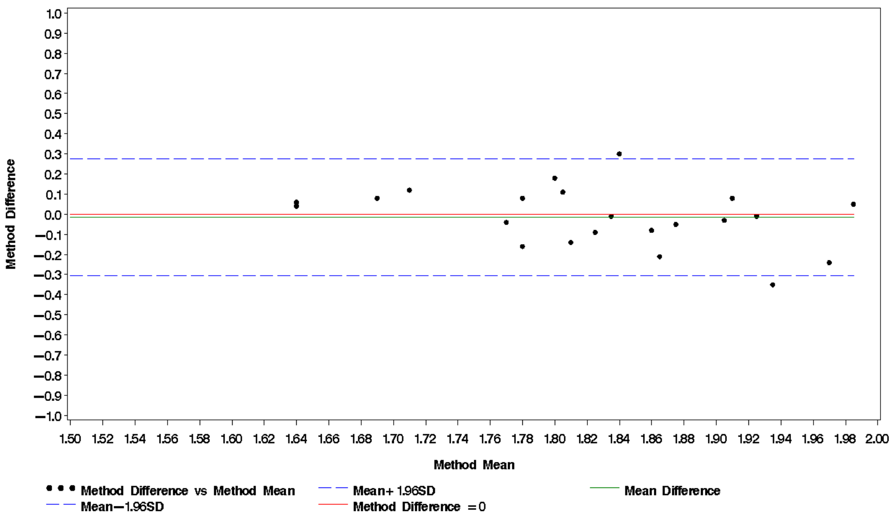

Figure 7. Bland and Altman plot comparing PAL_{mobile} and PAL_{ref}. The mean difference between PAL_{mobile}-PAL_{ref} was 0.014 (2SD 0.29). The regression equation was y=-0.58 x +1.05; r=-0.38; p=0.08.

PAL assessed using paper questionnaires

The Bland and Altman plots in Figures 8 and 9 demonstrate PAL_{quest1} and PAL_{quest2} compared to PAL_{ref}. The average PAL_{quest1} and PAL_{quest2} were slightly higher than average PAL_{ref} (1.84 and 1.90 respectively), neither of which were statistically significantly different from the reference data. The mean difference for PAL_{quest1} was 0.004 and PAL_{quest2} 0.07 compared to PAL_{ref}, with wider limits of agreement than for PAL_{mobile} (PAL_{quest1} 2SD=0.51 and PAL_{quest2} 2SD=0.90). Both questionnaires overestimated higher PAL values and underestimated lower PAL values as there was a statistically significant test for trend for both PAL_{quest1} and PAL_{quest2} (slope of regression line=0.79; p=0.04 and 1.58; p< 0.0001).

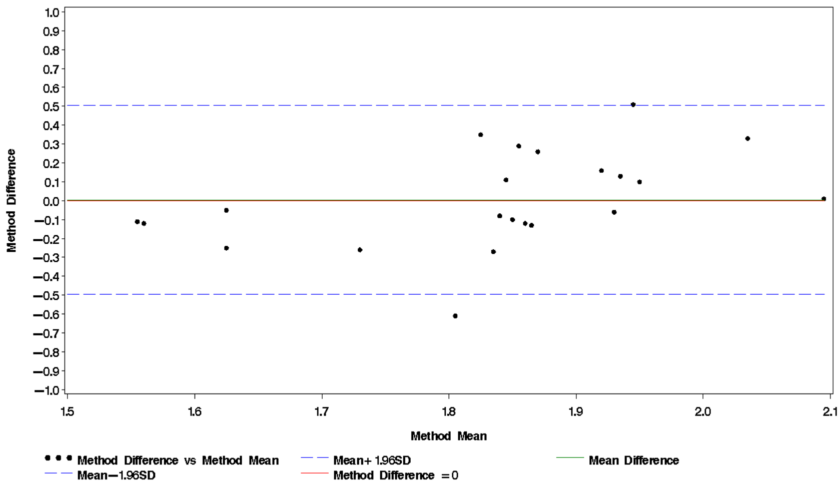

Figure 8. Bland and Altman plot comparing of PAL_{quest1} and PAL_{ref}. The mean difference for PAL_{quest1}-PAL_{ref} was 0.004 (2SD 0.51). The regression equation was y=0.79 x -1.45; r=0.44; p=0.04.

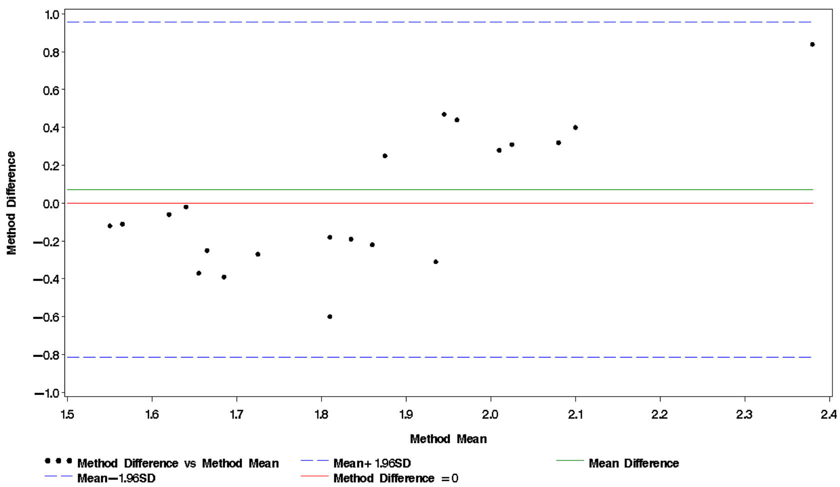

Figure 9. Bland and Altman plot comparing of PAL_{quest2} and PAL_{ref}. The mean difference for PAL_{quest2}-PAL_{ref} was 0.07 (2SD 0.90). The regression equation was y=1.58 x-2.88; r=0.65; p<0.0001.

Day to day variation in PAL obtained using mobile phones
PAL obtained using mobile phones varied considerably from day to day during the 14-day study period. The intra-class correlation coefficient for the 22 women was estimated to be 0.20, thus about 20% of the variation is between women while about 80% of the variation is due to day-to-day differences.

5.3 STUDY III

Response rate and socio-demographic distribution
Figure 6 demonstrates the attrition and drop-out among the SMS and the TI group. In the SMS group, mobile phone numbers were extracted to 1,055 (44% of total sample) individuals, out of which 187 (8% of total sample; 18% of contacted sample) declined participation after the initial invitation. During data collection, 344 of the contacted participants answered the first question, out of which 176 declined to continue the interview. In total, 154 participants answered all questions (6% of total sample; 15% of contacted sample). In the TI group, phone numbers were extracted to 1,636 (76% of total sample) individuals who were contacted through an invitation, out of which 1,193 (55% of total sample) were landline numbers and another 444 (21% of total sample) were mobile phone numbers. In the TI group, 183 (9% of total sample; 15% of contacted sample) declined participation after initial invitation. During telephone contact, 1,192 individuals were reached, out of which 176 declined to continue the interview after the first question and 1,009 (47% of the total sample; 62% of contacted sample) underwent the interview.

Figures 10 (A-D) demonstrate the distribution of gender, age, level of education and household size between the total sample, the contacted individuals and participants in the SMS group compared to the TI group. Distribution of gender was preserved between the participants in the original samples (Figure 10A). In the SMS group there was a shift toward the ages 18-39 years among the participants compared to the original samples and there is a clear under-representation of people above the age of 65 (Figure 10B). Highly educated individuals (>13 years of education) were somewhat more common among the participants in the SMS group than in the TI group (Figure 10C), and the proportion of one-person households was somewhat lower among the participants in the TI group compared to the original sample (Figure 10D). For both groups, family income and level of skill of occupation was somewhat higher among participants compared to the original samples. Widows/widowers were fewer among SMS-3, reflecting the deficit of elderly (Table 7). Among the original samples, approximately 30% had been admitted to a hospital at least once between 1999 and 2004. Though not statistically significantly different, the proportion with a recorded in-hospital episode was higher among participants in the TI group compared to participants in the SMS group. None of the participants had been hospitalitized for influenza.

After fitting a logistic regression model for non-participation in the total sample comparing allocation group SMS to TI, the crude OR was estimated to 13.1 (95% CI 10.4-16.7). After adjustment for all available background variables, OR shifted to 14.2 (95% CI 11.2-18.1) indicating a 14 times higher odds of non-participation in the SMS group compared with the TI group, with higher group difference in the higher age category. An interaction between allocation group and age was found (p=0.009). Analyzing subgroups by age, the adjusted OR in the age group 18-39 was 11.5 (95% CI 7.7-17.1), 16.4 in the age group 40-64 (95% CI 11.6-23.2) and 53.4 in the age group ≥65 (95% CI 18.4-155.4).

Vaccination coverage

Twelve individuals (8%) of the SMS participants said that they were vaccinated against influenza compared to 113 (11%) among the TI participants. A logistic regression model gave a crude OR of 0.7 (95% CI 0.4-1.3) of being vaccinated in the SMS group compared to the TI group. Adjusting for the demographic variables age, gender, education and size of household the OR shifted to 1.8 (95% CI 0.9-3.6). Though not statistically significant, most of this effect was seen after adjustment for age. No statistically significant interaction was found.

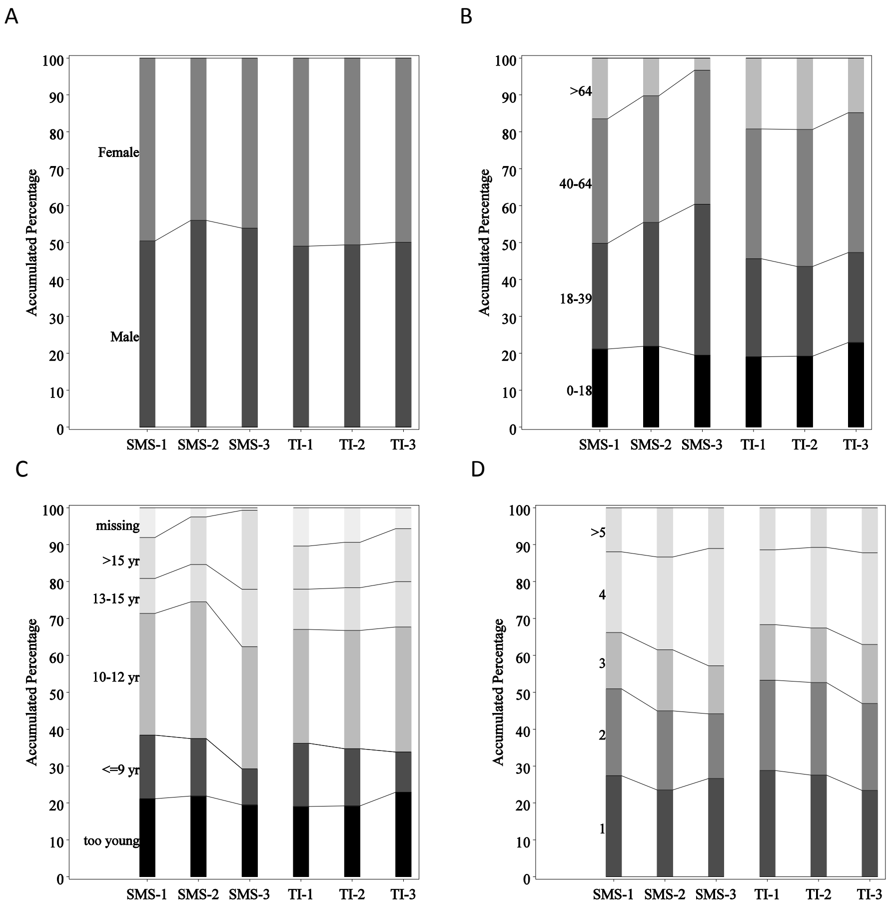

Figure 10 (A-D). The figures demonstrate socio-demographic characteristics in the total sample (SMS-1, TI-1), contacted sample (SMS-2, TI-2) and participants (SMS-3, TI-3). (A) Gender (B) Age group (C) Education and (D) Household size in a study comparing SMS and telephone interviews

Table 7. Distribution of background characteristics by mode of contact (SMS or TI). Within each allocation group, the original population sample was compared with the subset of individuals who could be contacted because a listed telephone number was found, and with the sub-subset of individuals who actually participated through answering the questions

	SMS			Telephone Interviews		
	Original sample n=2,400 n (%)	Contacted sample n=1,055 n (%)	Participants n=154 n (%)	Original sample n=2,150 n (%)	Contacted sample n=1,637 n (%)	Participants n=1,009 n %
Marital status						
Married/ Cohabiting	802 (33%)	346 (33%)	55 (36%)	765 (36%)	628 (38%)	406 (40%)
Single	758 (32%)	367 (35%)	55 (36%)	632 (29%)	439 (27%)	247 (24%)
Widow/ widower	113 (5%)	20 (2%)	1 (1%)	137 (6%)	113 (7%)	44 (4%)
Divorced	220 (9%)	91 (9%)	13 (8%)	207 (10%)	143 (9%)	81 (8%)
Living with parents	507 (21%)	231 (22%)	30 (19%)	409 (19%)	314 (19%)	231 (23%)
Occupation						
Military	5 (0%)	5 (0%)	2 (1%)	6 (0%)	4 (0%)	2 (0%)
Management/ Legislation	63 (3%)	30 (3%)	3 (2%)	74 (3%)	64 (4%)	43 (4%)
4th skill level	203 (8%)	103 (10%)	26 (17%)	199 (9%)	169 (10%)	129 (13%)
3rd skill level	219 (9%)	119 (11%)	22 (14%)	197 (9%)	169 (10%)	121 (12%)
2nd skill level	802 (33%)	374 (35%)	47 (31%)	710 (33%)	549 (34%)	329 (33%)
1st skill level	507 (21%)	231 (22%)	30 (19%)	409 (19%)	314 (19%)	231 (23%)
Missing*	601 (25%)	193 (18%)	24 (16%)	555 (26%)	368 (22%)	154 (15%)
Household income**						
High	726 (30%)	364 (35%)	67 (44%)	689 (32%)	567 (35%)	402 (40%)
Middle/high	502 (21%)	245 (23%)	26 (17%)	402 (19%)	322 (20%)	195 (19%)
Middle	462 (19%)	190 (18%)	30 (19%)	424 (20%)	319 (19%)	201 (20%)
Middle/Low	344 (14%)	134 (13%)	15 (10%)	288 (13%)	214 (13%)	111 (11%)
Low	315 (13%)	103 (10%)	16 (10%)	320 (15%)	197 (12%)	89 (9%)
Missing*	51 (2%)	19 (2%)		27 (1%)	18 (1%)	11 (1%)

* Data missing in the LISA register at Statistics Sweden.

** Income categorized as low (<14,915 €/ year), middle/low (14,916-24,129 €/year), middle (24,130-36,220 €/year) middle/high (36,221-50,415 €/year), high (≥50,416 €/year) and unknown.

5.4 STUDY IV

Response rate and socio-demographic distribution

Of the 14,000 invited individuals, 436 (3%) declined participation and 3,341 (24%) registered as participants; 1,297 (9%) through IVR and 2,044 (15%) through the web site. By the end of the study, 6,742 (49%) answered the final questionnaire. Compared to the total sample, women were over-represented among the participants (56% vs. 51%) and there was a shift toward older ages, which was especially obvious in the age group 18-39 (20% among participants vs. 30% in total sample). Figure 11 demonstrates the response rate in five years intervals (0-95 years) by gender. Participants also had a higher completed education, higher household income, somewhat higher representation of two-person households and a lower representation of individuals who had never been married. Table 8 demonstrates the distribution of socio-demographic characteristics between web and IVR participants. IVR and web participants, statistically significantly differed in regard to age, gender, education, household size, marital status and family income. Women, older individuals (>64 years), and individuals with a lower level of education were more represented in the IVR group, while participants younger than 65 years and those with a higher level of education were more represented in the web group. The web also attracted individuals from larger families, individuals with higher family income, and individuals who had never been married.

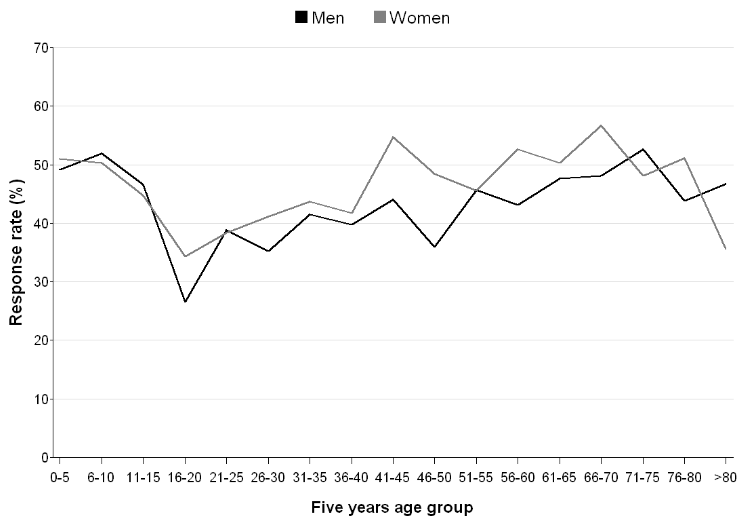

Figure 11. Total response rate by age (five years intervals) and gender to participate in a study of self-reports of upper respiratory tract infections

Distribution of reports

After 36 weeks, the system had registered 1,035 reports of infections from 617 (48% of 1,297) IVR participants. Out of these, 283 reports were identified as ILI from 229 (18% of 1,297) IVR participants. Among the web group, the system received 2,032 reports of infection from 1,107 (54% of 2,044), out of which 695 were identified as ILI from 460 (23% of 2,044) web participants. Figure 12 demonstrates the proportion of reported infections by study week and technique. Only one reported infection by participant is included in the figures. Corresponding data for ILI is not shown, but demonstrates a similar pattern. Both figures demonstrate the effect of the reminders, especially the one after Christmas. In stratified analyses, both men and women had a lower report frequency in the IVR group compared to the web-group. Figure 13 demonstrates the proportions of reported infections by 5-year age groups. Both the reported infections and ILI (data no shown) were higher among the younger age compared to the other age groups groups for both technologies. Table 9 demonstrates the crude RR for reporting at least one infection by technique and adjusted for available background information. The crude RR in the web group, relative to the IVR group, was 1.14 (95% CI 1.06-1.22). After including gender, age group, education, family size and income, the RR shifted to 1.01 (95% CI 0.94-1.09), indicating that the difference in reporting frequency between the two techniques was mostly due to other factors, and especially age group. The crude RR for reporting ILI was estimated to 1.27 (95% CI 1.11-1.47). After adjustment for available background factors the RR shifted to 1.08 (95% CI 0.94-1.25).

When studying the transfer between the two technologies, 103 (8% out of 1,297) IVR registered participants reported through the web and 129 (6% out of 2,044) of those who registered through the web had reported through IVR, indicating that most participants used the same technology for reports as for initial registration.

Table 8. Distributions of socio-demographic characteristics among participants who, respectively, used the web and IVR via telephone for initial registration to participate in a study of self-reports of upper respiratory tract infections

	Web n=2,044 n (%)	**IVR n=1,297 n (%)**	**p-Value**
Age group			
0-17	498 (24%)	229 (18%)	<0.0001[a]
18-39	480 (23%)	185 (14%)	
40-64	817 (40%)	430 (33%)	
≥65	249 (12%)	453 (35%)	
Gender			
Men	987 (48%)	486 (37%)	<0.0001[b]
Women	1057 (52%)	811 (63%)	
Education*			
≤9 years	179 (9%)	130 (10%)	<0.0001[a]
10-12 years	689 (34%)	444 (34%)	
13-15 years	379 (19%)	184 (14%)	
>15 years	734 (36%)	329 (25%)	
Missing	63 (3%)	210 (16%)	
Household size			
1	499 (24%)	417 (32%)	<0.0001[a]
2	442 (22%)	393 (30%)	
3	386 (19%)	150 (12%)	
4	495 (24%)	218 (17%)	
5	183 (9%)	96 (7%)	
≥6	39 (2%)	23 (2%)	
Marital status*			
Never married	700 (34%)	343 (27%)	0.0001[b]
Married	1081 (53%)	660 (51%)	
Divorced	214 (11%)	183 (14%)	
Widow/widower	44 (2%)	101 (8%)	
Missing	5 (0%)	10 (1%)	
Income**			
Low	123 (6%)	116 (9%)	<0.0001[b]
Low/middle	125 (6%)	171 (13%)	
Middle	288 (14%)	268 (21%)	
High/middle	337 (16%)	224 (17%)	
High	1137 (56%)	508 (39%)	
Missing	34 (2%)	10 (1%)	

*Children under the age of 17 were represented by the parent who reported in lieu of the child.

**Household income categorized as low (<14,915€/year), middle/low (14,916-24,129€/year), middle (24,130-36,220€/year) middle/high (36,221-50,415€/year), high (≥50,416€/year) and unknown

[a] Wilcoxon rank-sum test

[b] Chi-2 test

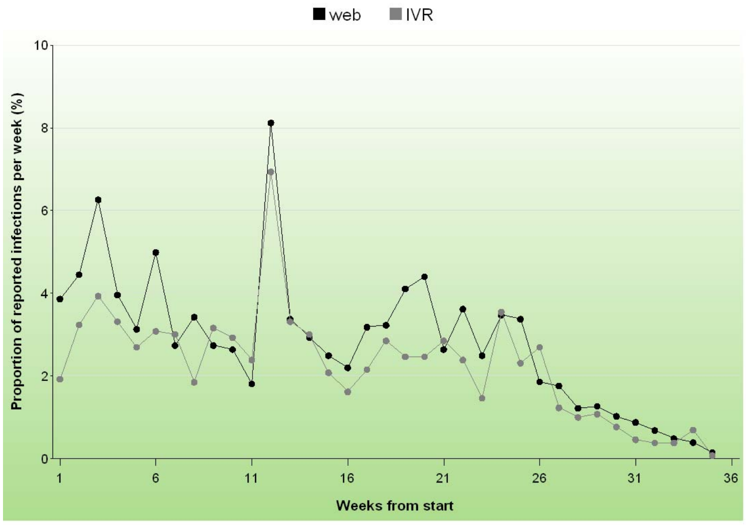

Figure 12. Proportions in the web and IVR groups that self-reported any infection during the influenza season 2007/2008, by week and reporting technology

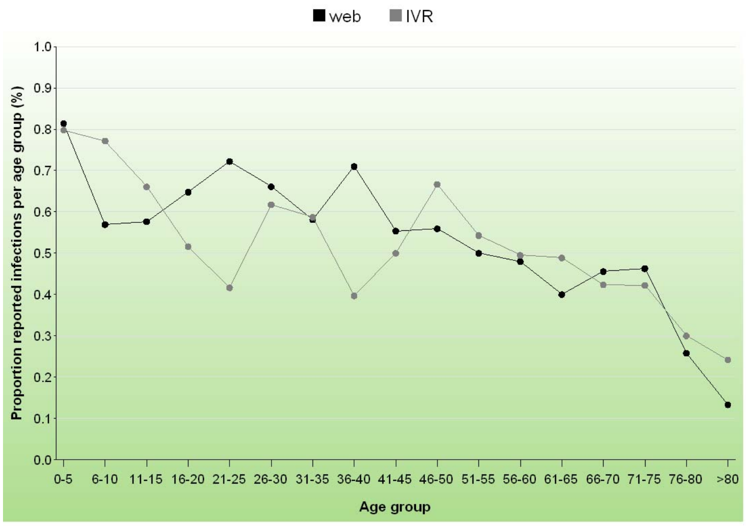

Figure 13. Proportions in the web and IVR groups that self-reported any infection during the influenza season 2007/2008, by 5-year age group and reporting technology

Table 9. Relative risks (RR) and 95% confidence intervals (CI) for reports of any upper respiratory tract infection, obtained using log-binomial regression. Results of univariable and multivariable models (the latter including all variables in the table)

	Univariable		Multivariable	
	RR	95% CI	RR	95% CI
Technique				
IVR	ref		ref	
Web	1.14	1.06-1.22	1.01	0.94-1.09
Age group				
0-17			1.36	1.18-1.57
18-39			1.23	1.08-1.41
40-64			1.06	0.94-1.20
≥65			ref	
Gender				
Women			1.24	1.61-1.33
Men			ref	
Education*				
≤ 9 years			0.91	0.80-1.04
10-12 years			0.94	0.87-1.02
13-15 years			1.12	1.03-1.21
>15 years			ref	
Household size				
1			1.03	0.81-1.32
2			1.00	0.78-1.27
3			1.03	0.82-1.31
4			1.07	0.85-1.34
5			1.04	0.81-1.32
≥6			ref	
Income**				
Low			0.93	0.81-1.08
Middle/Low			0.89	0.77-1.02
Middle			0.91	0.82-1.02
Middle/high			0.98	0.89-1.08
High			ref	

*Children under the age of 17 represented by the parent who reported in lieu of the child.

**Household income categorized as low (<14,915€/year), middle/low (14,916-24,129€/year), middle (24,130-36,220€/year) middle/high (36,221-50,415€/year), high (≥50,416€/year) and unknown

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

Cohort studies (studies I-IV)

The word cohort originates from the army and was originally a description of a Roman legion. Within medicine, a cohort is defined as a group of individuals sharing the same characteristics. In cohort studies, a group of individuals are followed over a specific time period with respect to exposure, where the exposed group is compared to an unexposed or reference group with respect to outcome of disease. The studies can be described as closed, where there are no entries and losses due to follow up after the study has begun, or open where the study subjects can enter and/or leave the cohort over the time period. Cohort studies and data collection during the study can be prospective or retrospective. A prospective cohort study is defined before outcome and follow-up has occurred and cohort members are followed over time with respect to exposure with uncertain outcome. In a retrospective cohort study, the study is defined retrospectively after both exposure and outcome have occurred, and retrospective data collection is based on events in the past. When possible, exposure data can be obtained through registers, enabling large studies with objective exposure information. In surveys where exposure data is based on recalls from study participants, retrospective data collection is sometimes based on memory and subjective perceptions. The reported exposure data might therefore be related to outcome, thus effected by bias (155). Therefore when exposure data is based on population-based data collection, prospective cohort studies are preferable. However, prospective studies need frequent follow-up in order to decrease losses during follow-up (156). Due to financial and logistic reasons, the studies are therefore often reduced to short time-periods where the outcome has a short latency and induction. Using digital methods during follow-up of cohort members reduces both logistical problems, but perhaps more importantly, the expenses, as once the system has been developed, there are often non or very small extra charges for additional contacts. This will enhance the possibilities for frequent contacts. In this thesis, cohort studies have been utilized in order to evaluate digital technologies in order to enhance the possibilities for both retrospective and prospective large-scale population-based data collection.

Validity

In epidemiological studies, the validity of the study can be affected by systematic and random error. Systematic error is caused by bias, leading to an incorrect association between exposure and outcome, whereas random error is the probability that the observed relationship between exposure and outcome is due to chance rather than a true association. There are a number of types of bias, including selection bias, observation bias and confounding bias and the effect varies, but once it has been introduced into a study it is difficult to remove. Therefore, it is important to carefully design the study in order to exclude the risk of bias. Internal validity depends on the presence of systematic errors and corresponds to the accuracy of measured association within the study population.

Selection bias

A major concern when using computerized methods in medical data collection is different selection forces resulting in different characteristics between participants and non-participants (4, 33). Selection bias is defined as a systematic error in inclusion criteria in a study, giving different association between exposure and outcome in those included in the analysis and those eligible (155). In a prospective cohort study, the study has been defined before the outcome has occurred thus selecting individuals on outcome is unlikely. Therefore, selection bias occurs mainly in retrospective cohort studies and case-control studies. Selection bias can occur in both prospective and retrospective cohort studies due to censoring after loss to follow up (157). These effects can in some cases effect the associations similar to confounding, but will here be discussed as selection bias. When using ICT in epidemiological data collection, there are two major reasons for selection mechanisms when recruiting a study population, as the participants first are selected by their knowledge and access to the chosen techniques (non-coverage), and as there has to be willingness and thus a motivation to participate (3). This selection threatens the representativeness of the study sample, both in terms of the proportion of those who are actually reached by the technique, but also the difference between respondents and non-respondents (4, 11). Though the influence by these selection mechanisms is not necessary known at the time of recruitment, it might later have an effect of the measured outcome. The difference between those who have and who don't have access to the Internet is often defined as the digital-divide (158). In the beginning of 2000, those who had access to the Internet were thought to be younger, wealthier and more well educated than those without, forcing selection of participants already during the inclusion phase (4). Comparison between web-based studies and other methods has demonstrated these differences (135). As access to the Internet and other ICT is still growing and is today accessible to most populations, the effect of the digital divide has probably been reduced. Especially when using mobile phones for medical data collection.

Non-response bias is a part of selection bias and occurs if participants differ from non-participants (4, 159). The consequence of non-response is only possible to determine if the denominator of the study frame is known. Hence, studies with an open invitation are not possible to study in terms of non-response, though these studies are probably affected by selection forces. Different studies have demonstrated that non-respondents often have lower socio-economic characteristics than respondents (e.g., lower completed education and lower income) (5, 160). Also gender and age are important factors for non-response, as women and older age groups tend to be loyal in epidemiological studies (30, 161). Introducing computerized technologies in follow-up of retrospective cohort studies which previously have used traditional methods for data collection might implement selection-bias, as individuals lacking the technology might differ from respondents.

When comparing respondents with non-respondents and declined participants in study I, the respondents were older. As hearing impairment is increased by age, the study might have attracted older age groups as these individuals are more concerned about their hearing capacity. This was also reflected by the self-estimated hearing as 52% of the 61 individuals who correctly completed all steps in the study had reported a hearing loss through the self-estimating hearing question. The willingness to participate was therefore probably biased toward self-selected individuals with an interest in the study topic. When comparing full respondents, with those who terminated the study after answering the questionnaire, having the correct version of Java and headphones at home seemed to have an effect for full compliance, indicating introduction of bias when forcing the study participants to complete these steps.

In study III, a population-based sample was randomized to be contacted either through SMS or through telephone interviews. In this study, there seem to have been and introduction of selection bias when forcing the participants to one of the two techniques, given the differences in response rates. In the SMS group, the non-response was in more than half of the study population not even voluntary, as these individuals was lost due to un-coverage in the telephone directory and thus never contacted by the study centre. When studying vaccination status, those who answered the questions through SMS were younger than those in the TI group, confounding the results. The different techniques might have introduces a selection bias in terms of willingness to answer the questions, thus effecting the outcome of vaccination in one or both groups.

When comparing studies III and IV, both studies attracted individuals with a higher completed level of education and a somewhat higher income compared to the total sample. Study IV also seemed to attract more women than men, and the response rate was very low among young adults. These selection forces have also been demonstrated in other epidemiological studies studying non-response (5, 30, 160, 161). In study III, the TI group had a higher inclusion of older individuals than the SMS group, indicating that older individuals prefer an established technique in favour of a newer. This was also demonstrated when comparing web and IVR in study IV, as registered participants in the IVR group were older than those who chose the web. This distribution among web participants compared to traditional methods has been demonstrated in other web-based studies (35, 162). Selection bias is a growing problem in many population-based studies (163), and using mobile phones and the web in data collection seems to exclude older generations.

Information bias

Information bias, or observation bias, occurs during data collection when there is a measurement error defining either exposure or disease (155, 159). Information bias is more or less evident in most epidemiological studies and can occur in both prospective and retrospective cohort studies, arising after the study subjects have entered the study. There are a number of different causes for information bias in population-based data collection, such as failure to follow up study participants, failure to recall and influences from the interviewer in interview-based data collection. In survey research, reporting bias is caused by systematic differences in collected information from study group and comparison group, and is an effect of failure in reporting from the study participants. In retrospective data collection, reporting bias can be an effect when demanding recall based on memory or due to the phrasing or misunderstanding of the question. Therefore, reporting bias can be, if possible, avoided by using data collected through objective methods not based on recalls from study subjects, such as medical records and registers, or by blinding of the study participants. But data can also be affected by reporting bias if the exposed group has a higher engagement in the study hypothesis than those who are unexposed. In interview-based studies, data might be affected due to influence of the interviewer, as study subjects tend to give more socially desirable answers to sensitive topics and report better health to self-rated health (16, 164). This bias is reduced by using self-administrated methods, and web-based studies have been demonstrated to be even less affected by misclassification on sensitive questions than paper questionnaires (15). On the other hand, in interview-based studies, the interviewer can explain misinterpreted questions to the respondent, and so decrease misclassification of the response. This is not possible in self-administrated studies, thus the quality of the questions is even more important. Information bias is often referred to as misclassification bias or measurement error, and can be divided into differential and non-differential misclassification. Differential misclassification can occur if an exposure or outcome is measured differently between two study groups, thus affecting the relationship between exposure and disease differently between exposed and unexposed. Differential misclassification can be very serious as the misclassification will bias the results toward infinity, thus increasing the difference between the two study groups. Both studies I and II aim to develop techniques and methods to decrease the risk of introducing misclassification. In study I, if those who have experience heavy gunshot report greater hearing loss due to knowledge of the risks compared to those who have not, a subjective self-estimating question might introduce differential misclassification of disease. The hearing test was therefore developed as an objective method for studying the effect of heavy gunshot on hearing capacity. In study II, questionnaire II indicates a differential misclassification in reporting of physical activity as those who were highly active reported too high physical activity compared to the reference, and those who had a low physical activity level according to the questionnaire tended to underreport compared to the reference. In study III, the participants were blinded to the questions prior to the interview. However, those who were vaccinated against influenza might have had a lower tendency to terminate the session hence biasing the reports. In study IV, differential misclassification might have been introduced during the study due to failure to follow-up that would have affected the denominator, as a result misclassifying diseased as non-diseased due to lack of information. However, as this study compared web against IVR, this loss is differential or non-differential depending on the magnitude of the loss in both groups. Non-differential bias occurs randomly and does not affect the relationship between exposure and outcome, thus the bias will give a diluting affect to the results. Studies III and IV probably attracted highly motivated participants who might have different response patterns compared to the non-respondents, which might influence reported health behaviours.

Confounding

Whereas information bias and selection bias is the result of an incorrect sample or invalid study design, confounding results from associations that occur naturally in the general population Confounding occurs when the association between an exposure and a certain outcome results by the uneven distribution of a third variable between the exposure groups. By theoretical definition, such a third variable, a confounding factor, has to be associated with the exposure, while at the same time an independent cause or predictor of the outcome. It also must not be an intermediate in the causal pathway between the exposure and the outcome.

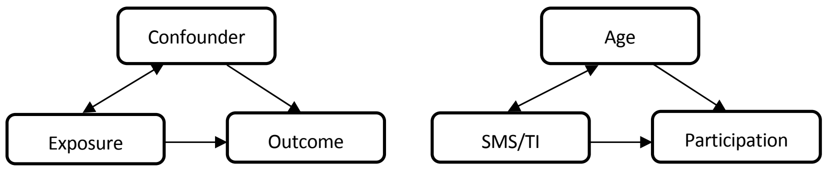

Figure 14. Confounders and the relationship to exposure and outcome

Given that confounders have been measured properly, researchers can control for confounding either during the study design or in analysis of the study. During the study design, confounding is reduced by randomization, where the study participants are randomly selected in either the exposed or the unexposed group; restriction of the study population by for example gender or a specific age group; or through matching, where the participants in the exposed group are matched to those in the unexposed based on potential confounding factors preventing confounding of crude estimates. In the analysis, confounding can be controlled for by standardization, stratification or through multivariate analysis. In stratification, one stratifies the analysis by the confounding factors in order to measure the effect of the variable, and if so, adjust the results by pooling the estimates. Standardization is weighted averages of occurrence measures. In this thesis, when exposure and outcome were defined, confounding was controlled for through multivariate analysis discussed in section 4.3. The disadvantage of multivariate models is that one loses visual context of the data and the analysis is only valid as long as the model fit the data. On the other hand, a multivariate analysis can control for many confounding factors at the same time. Even though the Internet-based hearing test in study I has the potential to reduce information bias through collecting objective measures rather than subjective self-estimates, age is a potential confounder, as age could affect both prior hunting experiences and hearing capacity. In both studies III and IV, age and education confounded the data. The relationship between being allocated to the SMS group or the TI group, participation in the study, and age is demonstrated in Figure 14. In this study, the chance of localizing an individual through SMS in mobile phones was decreased by age, while the chance of participating in the SMS group was decreased by age. High education increased the chance for both having a mobile phone and participating in the study. Similar confounding effects were demonstrated when adjusting data on vaccination status by allocation group. In study IV, the chance for reporting infection was decreased by age, while the chance for choosing the web as the reporting tool was decreased by age.

Effect measure modification

Effect measure modification is introduced in a sample if estimates differ between stratums defined by a third variable. Effect measure modification is sometimes referred to as effect modification or interaction. Compared to confounding, effect measure modification is not a nuance which should be eliminated, but is rather an interesting phenomenon which should be investigated further and described. In study

III, there was evidence of effect measure modification between age and non-participation in the SMS and the TI group, indicating a difference in the association between allocation group and non-participation and increasing by age over the different age strata.

Precision

Precision can be described as the lack of random error and the associations resulting by chance (165), and can be increased by increasing the study sample size. In survey research, study precision can be severely affected by low response rates and is a growing problem. Precision can be statistically evaluated by p-values and confidence intervals, which are effected by sample size and strength of study association. Wide confidence intervals indicate low precision. All studies in this thesis are pilot studies with relatively small sample sizes, influencing the precision of the results. In studies I, III and IV, the precision was further decreased from poor response rates. The low response rate gave particularly low precision when comparing vaccination status among SMS and TI groups in study III. In study IV, the number of participants was relatively high in both the IVR and the web group; however, a season with low incidence of influenza might affect the weekly precision. In study II, 22 participants is very low number of individuals for epidemiological studies. But the high accuracy of the reference data from the DLW method increases the validity of the study, though precision would have been increased with a larger sample size.

Generalizability

Generalizability is referred to as external validity (33), and applies to whether the study results can be applicable to a broader context outside the study population. In epidemiological cohort studies, it is often difficult to generalize the results to other populations as the results are often restricted to the inclusion criteria of the study. These restriction criteria are often implemented in order to control for confounding in the study. Within development of new methods for data collection, there are concerns regarding whether the technologies force selection toward individuals with specific characteristics. In study II, the women were recruited to participate in a study about energy expenditure and metabolism. During the two week study period, the women tested two different accelerometers, one pedometer and one heart-rate meter at the same time as they collected urine samples for the DLW and submitted daily reports via mobile phones. The group is therefore highly motivated and self-selected due to interest in the study questions. This might also have affected the motivation to answer the mobile phone questions resulting in the high compliance. The impact of a possible selection mechanism is however difficult to determine as the women were recruited through advertisement and there is no reference group to this data. Similar selection mechanisms are seen in the other studies and the generalizability of the collected data are strictly speaking limited to the characteristics of the participants. As participants differed from non-participants in terms of socio-demographic patterns, the results should be repeated in other populations before they can be generalized to a larger context. As the Swedish population has high accessibility to the techniques used in this study, the results might not be applicable to populations with other prerequisites.

6.2 FINDINGS AND IMPLICATIONS

Study I

In study I, the feasibility of using an Internet-based hearing test among a cohort of Swedish hunters was evaluated. In order to participate in the study, the participants were obliged to complete a web-based questionnaire, have installed the correct version of Java, possess headphones and find a younger individual for calibrating the test. The low response rate (16%) was therefore not unexpected, though it expresses the difficulty of using the test in a population-based setting. The study attracted highly motivated individuals, which decreases the possibilities to generalize any results to other populations. The largest reason for declining participation was probably unwillingness and lack of interest in the study question. One major weakness of the study was the need to calibrate the hearing test against a reference person, as 27 (31% out of 88) tests had to be excluded due to incorrect calibration. During closer evaluation of the calibration data, some of the hunters had used an individual with decreased hearing capacity for calibration and some had randomly set the bar for calibration without a reference individual. This has however been adjusted for future studies.

The results from the hearing test were compared to the self-estimated hearing question. This comparison was executed in order to evaluate the need for a more objective tool for measuring hearing. The results from the hearing test and the self-estimated hearing were statistically significantly different ($p<0.001$) and the Internet-based hearing test indicated a hearing loss in 20% of the tested individuals, compared to 52% in the self-estimated question. Though being exposed to extreme noise, due to the relatively young age of the participants (20-60 years), the high prevalence of hearing impairment from the self-estimated hearing is very high (166). This might indicate a need for more objective measurement for hearing impairment. Though the hearing test has a number of limitations, it is a novel tool for measuring hearing capacity in population-based settings and demonstrates the possibilities of using the Internet in epidemiological data collection.

Study II

In study II, repeated measures of physical activity through a Java-based questionnaire in mobile phones were evaluated against the gold standard, the DLW-technique and indirect calorimetry. The mean PAL from the mobile phones was not statistically diverse from the reference PAL, and according to the Bland and Altman plot the difference between the two methods was small with small limits of agreement. When comparing the reference data to two formerly used questionnaires, the mean difference was small but with wider limits of agreement. The difficulty in measuring physical activity through self-reports was highlighted in a review by Nielson et al. in 2008 which concluded that most retrospective questionnaires on physical activity have low or very low agreement against DLW (123). Other studies have indicated better measurements with physical activity records, but these are prone to difficulties in compliance. As mobile phones are today a part of daily life and have built in technique for reminders, the device has the potential to increase compliance in data collection through daily records. In this study, only two of the 22 women forgot one respective two reporting occasions. Also, as the device is connected to the Internet, all data can almost immediately be transferred to the study centre.

This study technique is limited to mobile phones supporting Java. This is a limiting factor in a population-based setting, as this software is restricted to newer mobile phones. In this study, 64% of the women could download the program to their mobile phones. In an unpublished study from spring 2007, where mobile phone access was investigated among 95 individuals, 60% had mobile phones supporting Java. According to the leading mobile phone distributors, most individuals change mobile phone every other year. Therefore, this limitation is probably decreased every year, though Java might be exchanged for other scripts.

This study shows that mobile phones are useful tools for repeated collection of PAL values and the procedure for data collection on physical activity has a great potential in large-scale prospective epidemiological studies. The mobile phone-based procedure could also be used for other purposes where variation could be decreased by repeated measurement, such as assessment of energy intake or other health-related variables.

Study III

Study III aimed at evaluating the feasibility of collecting influenza vaccination status among the Swedish population through SMS in mobile phones. Out of the 2,400 randomly selected individuals for contact through SMS, 154 (6%) answered the questions. This is an almost unacceptably low response rate in epidemiological studies. The biggest decline was due to low yield of mobile phone numbers after linkage to the telephone directory, as only 44% of mobile phone numbers were found. However, similar difficulties were found when locating landline phone numbers in the TI group as only 55% of the phone numbers could be found in this group. This demonstrates the difficulty in locating telephone numbers and a need to evaluate telephone-based methods in epidemiological studies. In the SMS group, up to seven mobile phone numbers were found for one individual that further increased the difficulty in reaching the target individual. When comparing vaccination status between the SMS group and the TI group, the differences between the two groups were rather an effect of age than the actual technique. These results could however be due to chance considering the low power among the SMS group.

There were a number of limitations in the study design which should be pointed out prior concluding the results. First, the participants were contacted through a number before the research group had determined whether the number was in use or not. Out of the 868 who were contacted through the SMS, 524 never contacted the research centre. The reason for this is not known. Accordingly, the SMS was sent at 5 pm when many individuals are in transit and from a foreign number which the participants did not recognize. At the time of the study, the study centre could not pay for the three SMSs, so many participants probably chose to not participate due to cost. The low yield of telephone numbers demonstrates a need for new methods for contacting individuals. This study displays a shift in telephone habits and mobile phones cannot be neglected in population-based data collection. Though the study has a low power, the SMS gathered information on vaccination status that was not statistically significantly different from information gathered via telephone interviews.

Study IV

Study IV aimed at comparing the use of IVR and the web in a population-based surveillance system for respiratory tract infection including ILI. Both techniques were included in the study in order to reach also those who do not have access to the Internet. After recruitment, two thirds of the participants had registered through the web. Web participants differed from IVR participants in terms of socio-demographic features. These differences have been demonstrated in previous epidemiological studies comparing the two techniques and comparing telephone interviews with the web (15, 135). When comparing reporting frequencies, there were more reports through the web compared to IVR both for any infections and ILI. After adjustment for available background factors, these differences were not statistically significantly different for either any infection or ILI. As for study III, the largest effect was seen after adjusting for age.

As the study attracted individuals with a comparably high socio-economic status, the results might be affected as this might indicate healthy individuals (30, 135). But the web group reported more infections compared to the IVR group, which undermines this theory and indicates that these health advantages might not affect common cold and influenza. On the other hand, the web group contained larger families and reports from younger individuals and children who are notorious vectors of infections (167). The IVR group were more represented by older age groups who are interacting less with children and are included among the risk groups who are recommended vaccination against influenza (168, 169).

A population-based system based on traditional methods for data collection would be ineffective both in terms of time delay, costs and logistical issues. Using ICT increases the possibilities of monitoring infectious diseases through self-reports. Through a common Costumer Relationship Management (CRM) system, more than one technique can be implemented in the system increasing the accessibility to a larger part of the population. Though the same socio-demographic characteristics determining registration to the system were factors for reporting infections, the techniques did not seem to influence the results.

7 CONCLUSION AND IMPLICATIONS FOR THE FUTURE

In this thesis, the WWW, mobile phones and IVR were evaluated as tools in epidemiological data collection among the general population. Studies I, II and IV describe means for epidemiological data collection beyond traditional contexts, while study III validates e-epidemiological data against a traditional method. Except for study II, all studies were affected by low response rates, in particular among men between 20 and 30 years, which influence both precision and validity of the study results. The low response rates are probably an effect of study design, but also a general trend in epidemiological studies, and especially the decreased in response rate among younger men should be addressed in order to ensure representativeness in future studies. Using a mixed-mode between two or three techniques could increase these response rates, and both studies III and IV indicate that the older age group still prefer traditional approaches, addressing the benefits of using a mixed-mode design. All studies were affected by bias and all but study II were probably confounded by age. The mechanisms behind these factors are important to evaluate further in order to understand how they affect the collected data and how to address these factors in future studies. However, when possible to adjust for confounders, the techniques per se did not seem to influence the collected data negatively compared to reference data.

Sweden has one of the highest accesses to both the Internet and mobile phones in the world, why these results might not be generalizable to populations with lower access. Though the mobile phones are accessible to a larger part of the world, the results from the mobile phone studies should be repeated before applying the results to other populations, as mobile phone habits and conditions for payment differ over the world. However, these differences will probably decrease as more population become more computerized by time.

The results from this thesis have verified many of the results from previous epidemiological studies using ICT, such as distribution of socio-demographic characteristics between respondents and non-respondents and between the new techniques and traditional methods. The studies also demonstrate the possibilities of using ICT in epidemiological data collection, both compared to established methods but also beyond traditional contexts. Once contact has been established, using continuous self-administrated computerized tools such as the web and mobile phones allow data to be collected more frequently and decrease bias due to retrospective recalls (3). This increases the possibilities for large scale data collection in prospective epidemiological studies running over several decades. This thesis includes a fraction of the possibilities of using ICT in epidemiological data collection and e-epidemiology is still in its youth. Once the techniques have been thoroughly evaluated, there are probably endless possibilities to ensure high quality data collection through methods adapted to a modern society.

8 SVENSK SAMMANFATTNING

Traditionella metoder för insamling av medicinsk data är personliga intervjuer, telefon intervjuer och pappersenkäter. Dessa metoder är validerade och ger ofta tillförlitliga data, men är samtidigt kostsamma och tidskrävande och är därför mindre lämpliga för storskaliga studier och vid insamling av stora datamängder. De senaste decennierna har svarsfrekvenserna i epidemiologiska studier sjunkit, vilket ökar risken för skevhet i studiepopulationen och minskar generaliserbarhet av studieresultat. Detta påvisar ett behov av nya metoder för epidemiologisk datainsamling. Digitala teknologier, såsom Internet, mobiltelefoner och interaktiva röstmeddelanden (IVR) har de egenskaper som kan öka förutsättningarna för storskalig datainsamling, samtidigt som teknikerna kan användas för datainsamling som tidigare inte varit möjlig. Den här avhandlingen omfattar fyra studier där Internet, mobiltelefoner och IVR använts.

I studie I har ett Internetbaserat hörseltest och en webbaserad enkät utvärderats i en kohort av Svenska jägare. Studien gav en låg svarsfrekvens och de individer som valde att delta i studien var äldre och hade större tillgång till rätt utrustning än de som inte deltog. Trots att studien hade ett flertal begränsningar visar den på möjligheterna att använda digitala metoder i medicinsk datainsamling. I studie II utvärderades upprepade mätningar av fysisk aktivitet via en Javabaserat enkät i mobiltelefoner mot en gyllene standard för mätning av energiförbrukning. De upprepade mätningarna i mobilen visade sig ha god överrensstämmelse mot referensdata och att använda mobilen i mätning av fysisk aktivitet kan vara en kostnadseffektiv metod för storskaliga studier. I studie III samlades data om influensavaccination in via SMS och jämfördes med data insamlat via telefonintervjuer. Studien genererade väldigt låg svarsfrekvens, men efter justering av övriga variabler gav SMS-data samma resultat som det insamlat via telefonintervjuer. I studie IV ombads en frivillig grupp individer att självrapportera symptom av luftvägsinfektioner och influensa liknande symptom antingen via webben eller via IVR. Vid jämförelse av deltagare som anmält sig via de olika metoderna visade det sig att webben lockade fler män och yngre individer med högre utbildning än IVR. När de olika rapporterna jämfördes fanns det ingen skillnad mellan de två teknikerna efter justering av övriga variabler.

Studie I, III och IV hade väldigt låga svarsfrekvenser, vilket påverkar studiernas validitet och precision. Alla studier var påverkade av skevhet, och alla förutom studie II var förmodligen förvillade av ålder. Om metoderna ska användas i framtida studier är det viktigt att dessa mekanismer utvärderas för att förstå hur de påverkar insamlat data. Men då det var möjligt att justera för övriga variabler verkade det som att teknikerna i sig inte påverkade resultatet. Alla studier har utvärderats i Sverige och då det Svenska folket har väldigt stor tillgång till digitala tekniker kan resultaten eventuellt inte generaliseras till populationer där förutsättningarna är annorlunda. Den här avhandlingen inkluderar en bråkdel av de möjligheter som digitala metoder ger i epidemiologisk datainsamling och när teknikerna blivit utvärderade kan de förmodligen leda till oändliga möjligheter för framtidens epidemiologiska forskning.

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