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COHORT PROFILE

Cohort Profile: The Danish Web-based Pregnancy Planning Study—'Snart-Gravid'

Ellen M Mikkelsen,[1]* Elizabeth E Hatch,[2] Lauren A Wise,[3] Kenneth J Rothman,[2,4] Anders Riis[1] and Henrik Toft Sørensen[1,2]

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How did the study come about?

The Danish Web-based Pregnancy Planning Study was initiated in 2007 by researchers from Aarhus University Hospital, Denmark and Boston University, USA, primarily to evaluate the feasibility of Internet-based recruitment and follow-up of a cohort of reproductive age women. In this report, we describe the study design and present descriptive data based on the pilot phase of this ongoing study.

Several large-scale cohort studies of reproductive age women have been conducted, including the Danish National Birth Cohort[1] and The Norwegian Mother and Child Cohort Study.[2] These studies, however, have included women already pregnant and have collected either retrospective data on exposures during the preconception period or no such data. Volunteers for cohort studies are often recruited in clinical, school or work settings where potential participants can be readily identified; however, women planning to conceive are a diverse group that cannot be easily recruited from one particular setting. In addition, many women do not advertise their attempts to become pregnant.

Using the Internet for recruitment requires that potential participants have access to the Internet, but in return the venue for recruitment is broadened and the need for in-person contact in the recruitment process is eliminated. Furthermore, potential participants can volunteer without disclosing their plans to become pregnant to anyone face-to-face. Conducting traditional birth cohort studies is expensive in terms of both time and money and often hampered by a large proportion of drop outs.[2,3] Using the Internet for recruitment and data collection avoids the expense related to a physical encounter, such as printing questionnaires, postal fees, in-person interviews, etc. In addition, maintaining contact with the participants by individual e-mails and 'shared messages' posted on the website may reduce attrition. Thus, the Internet has the potential to become a key tool for cohort recruitment and follow-up in epidemiologic studies.

Being able to conceive and to become parents is an important life goal for most people. A decrease in human fertility has been observed in several western nations; its causes are likely multifactorial.[4–9] It is well documented that fecundity decreases with age[10,11] and a large number of lifestyle and behavioural factors have been hypothesized to be associated with subfecundity.[12–16] Lifestyle exposures such as smoking, caffeine and alcohol consumption, increased body mass index (BMI), use of NSAIDs and oral contraceptives are frequent among reproductive age women.[17–19] Understanding the possible role of these factors in relation to subfecundity is thus an important public health goal, but questions remain about the effect of several of these exposures either because few studies have been undertaken (BMI, NSAIDs and oral contraceptives) or because previous studies have shown mixed results (alcohol,[15,18,20] caffeine[21,22]). In addition, the majority of the studies to date have been retrospective [12,15,21,23] and susceptible to a variety of biases affecting time-to-pregnancy (TTP).[24]

Another area of public health interest is whether some of these preconception exposures affect risk of miscarriage or infant birthweight. For example, only two studies have evaluated the relation between NSAID use and miscarriage, with both studies reporting a positive association and speculating on possible mechanisms of action.[8,25] Similarly, one study of 304 pregnant women reported that oral contraceptive use was strongly associated with higher birthweight.[26] In these studies however, data on

[1] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.
[2] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA.
[3] Slone Epidemiology Center, Boston University, Boston, MA, USA.
[4] RTI Health Solutions, Research Triangle Park, NC, USA.
* Corresponding author. Department of Clinical Epidemiology, Olof Palmes Alle 43-45, 8200 Aarhus, Denmark.
E-mail: em@dce.au.dk

preconception exposures were collected retrospectively[25,26] or were incomplete because NSAIDs purchased over the counter were not included.[8] Thus, these findings ought to be replicated in a prospective study including more detailed information on exposures.

What does the study cover?

The initial aims were (i) to assess both feasibility and validity of conducting studies that rely on use of the Internet to recruit and follow volunteers in prospective epidemiologic studies; (ii) to evaluate prospectively the relation between several lifestyle and behavioural factors and delayed TTP among women attempting to conceive; and (iii) to evaluate the relation of several exposures to risk of miscarriage and infant birthweight among women who conceive.

Who is in the sample?

We began enroling women into the Danish Pregnancy Planning Study on June 1, 2007. The source population for the cohort comprises women of reproductive age in Denmark. After 6 months 2368 participants were enrolled, with 5000+ expected by December 1, 2008. As there are more than 65 000 live births per year in Demark (The Danish Birth Registry, 2005), our aim of recruiting 5000 participants in 18 months appears achievable.

Participants are recruited primarily through a pop-up advertisement placed on a nationally well-known health-related website (www.netdoktor.dk.). In addition, recruitment is enhanced by a coordinated media strategy that included a press release that attracted attention from print media, online news sites, television and radio.

Enrolment and primary data collection are achieved solely via the study website and with e-mail.

The study website is designed to be inviting and informative, explaining the aim of the study and participation criteria. Participants are not offered any incentives for their contribution other than links to other websites relevant to women wanting to become pregnant.

Potential participants who are directed to the study website or who come upon the study website are required to read a consent form and to fill in a screening questionnaire to confirm eligibility before enrolment. Participants also have to provide their civil registry number (CPR) and e-mail address in order to enrol. To be eligible, women have to be 18–40 years of age, Danish residents, in a stable relationship with a male partner, attempting to conceive (but not for longer than 12 months) and not using any type of fertility treatment. Women currently using birth control but otherwise eligible for the study who plan to discontinue birth control within the next 6 months in order to become pregnant are asked to provide their email address for later recruitment.

How often are cohort volunteers contacted?

After completing the baseline questionnaire participants are contacted bimonthly by e-mail for 12 months or until conception has occurred. If necessary, two email reminders are sent at each follow-up. Women who conceive will be asked to complete one questionnaire during early pregnancy, after which active follow-up cease. In addition, at each follow-up the participants are asked if they are still trying to conceive and if not they are withdrawn from the study. The study website provides information on how a participant actively can leave the study in order not to receive further emails.

Every birth that takes place in Denmark after gestational age 20 weeks is registered in the Danish Birth Registry.[27] From this registry primary outcome data (birthweight, gestational age, stillbirths) on all clinically confirmed pregnancies in the cohort will be obtained. Information on all miscarriages leading to treatment in hospitals or outpatient clinics will be obtained from The Danish National Hospital Register[28] and information on induced abortions will be obtained from The Induced Abortion Registry.

What variables are measured?

Data will be obtained both with self-reported questionnaires and from a number of nationwide registries. In Denmark, the CPR number is a unique 10-digit personal identification number assigned to each resident by the Central Office of Civil Registration.[29] The Danish Central Person Registry is continuously updated with information regarding vital status and change of address of all residents. This CPR number enables us to link questionnaire data with extensive data on health outcomes, exposures and socio-demographics that are routinely recorded in nationwide population registries.[29]

The following self-reported data are obtained from the web-based questionnaires:

(I) Socio-demographic data, including age, partner's age, years of education, type of education and income.
(II) Reproductive and medical history including data on menstruation, pregnancies, miscarriages, parity, age at each birth, previous use of contraception, medication use, medical illnesses and history of fertility problems for participant and partner.
(III) Lifestyle and other factors, including height and weight, partner's height and weight, waist and hip circumference, alcohol and caffeine consumption, smoking habits of participant and partner,

frequency of intercourse, physical activity and occupational exposures.

The following registries will be used to obtain relevant outcome and exposure data in addition to self-reported data for control of confounders:

(I) The Danish National Registry of Patients contains detailed information, including date of admission and discharge, and up to 20 discharge diagnoses and procedures for all patients who have been admitted to a somatic hospital in Denmark since 1977, including all outpatient and emergency contacts since 1995.[28]
(II) The Danish Birth Registry comprises data on all births in Denmark.[27] The main data are gestational age, length and weight of infant, birth complications for the mother and the child and procedures executed during labour.
(III) The Register of Legal Induced Abortion comprises data on all legal abortions since 1973 including gestational age.
(IV) The Danish Prescription Database comprises data regarding type of drug and date of prescription on all prescriptions filled in Denmark since 1995.
(V) The Integrated Database for Longitudinal Labour Market Research includes comprehensive socio-economic data regarding the education, employment and income of the entire Danish population.
(VI) The In Vitro Fertilization (IVF) Registry includes information on all IVF treatments, which take place in Denmark. Apart from treatment data, the Registry also contains information about the outcome of all IVF pregnancies.

What is the attrition?

After 6 months of recruitment (June 1, 2007 through December 1, 2007), the study website had more than 100 000 hits and more than 48 000 unique visitors. Figure 1 shows that the number of enrolled women per week was largest during the first weeks when the study was introduced in the media and the advertisement was initially placed on the website www.netdoktor.dk. During the last few months of the pilot period, enrolment stabilized at around 40–50 new participants per week. Three-quarters of the participants reported they had heard about the study from the Internet, 20% became aware of the study through newspapers or magazines and about 5% had heard about the study in radio/television or by word of mouth.

After 6 months, 4807 women had completed the screening form (Figure 2). Of these, 1737 (36%) did not meet the eligibility criteria for the study. Among the remaining 3070 women, 702 did not provide their CPR number, leaving 2368 to be randomized to complete either a long or short version of the baseline questionnaire. At baseline, 80 women did not complete the questionnaire. Thus, 2288 women in total were enrolled in the cohort.

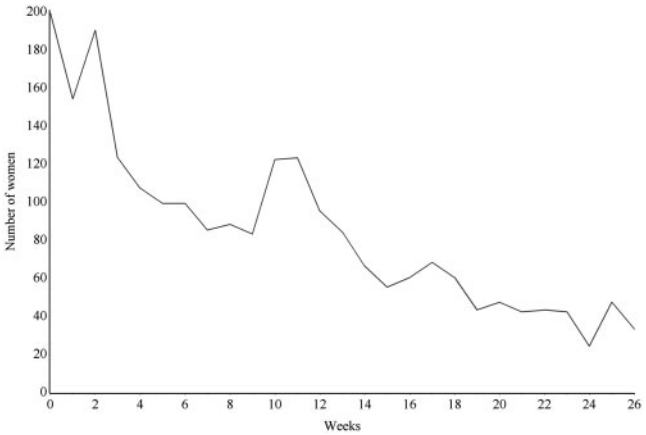
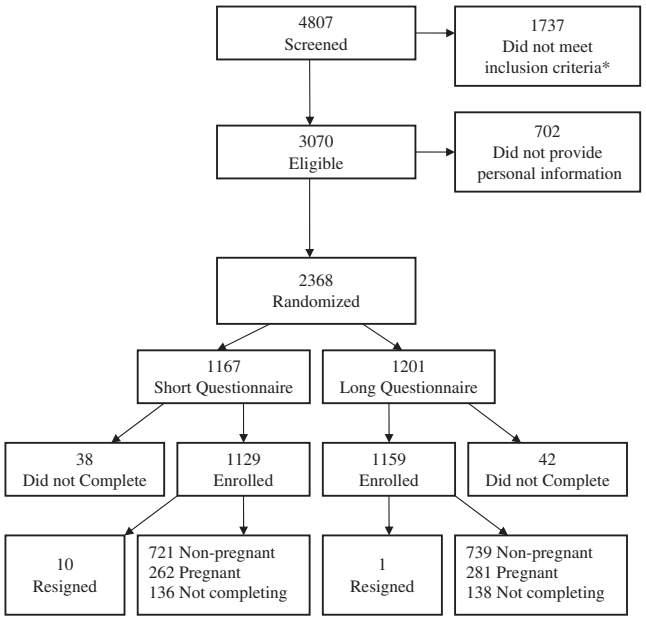


Figure 1 Number of participants enrolled per week. Zero week: study launched along with press release; 2 weeks: advertisement placed on www.netdoktor.dk; 10 weeks: article in a large women's magazine



* Inclusion criteria–(number excluded due to at least one criterion)

- Age (≥18 years and <41 years) ($n = 29$)
- Female ($n = 32$ male)
- Partner ($n = 72$ no partner)
- Not using birth control ($n = 586$ using birth control)
- Trying to become pregnant ($n = 142$ not trying right now)
- Pursued conceiving ≤12 months ($n = 952$ tried >12 months)
- No fertility treatment ($n = 427$ in fertility treatment)

Figure 2 Flow chart of The Danish web-based pregnancy planning study—'Snart-Gravid'

At the first follow-up after 8 weeks, 2003 (87.5%) of the 2288 enrolled women completed their second questionnaire. Of the enrolled women, 543 (23.7%) had become pregnant, 11 (0.5%) had actively resigned from the study, and 274 (12.0%) did not complete the questionnaire. The latter may not all be lost

to follow-up as they may complete a later follow-up questionnaire. Overall, the recruitment and low attrition in this web-based cohort study are very promising.

What has been found so far?

To evaluate the effect of questionnaire length, all eligible women were randomized with equal probability to fill either a long or short version of the baseline questionnaire. The results show that overall few data items were missing and the questionnaire length did not influence participation or missing data.[30]

Median age for participants enrolled during the first 6 months of the pilot period was 28.9 years and 31.0 years for their partners (Table 1). More than 75% of the participants had 12 years or more of basic schooling and 55% had additional education of 3–5 years. The total household income exceeds DKK 40 000/month (€8300) for more than 55% of the participants and their partners. The majority (56%) of participants had been trying to conceive for 2 months or less, and 17% had been trying to conceive for 7–12 months (Table 2). The largest proportion of participants (65%) was planning their first child. Regarding sexual intercourse, 47% of participants reported a frequency of two to three times per week.

Birth control pills were by far the most frequent type of contraception used last by the participants (55%). Condoms were used by 19%. Only 5% of the participants had never used birth control pills. The majority had tried two or more different brands of birth control pills. As regards lifestyle characteristics, 14% of the participants smoked daily whereas 21% of their partners were daily smokers. Almost one-quarter of the participants did not consume any alcohol and

Table 1 Baseline characteristics of enrolled women and their partners

Characteristic	$N = 2288$
Age, median (25th–75th percentile)	28.9 (26.3–31.9)
Partner's age, median (25th–75th percentile)	31.0 (28.0–34.0)
Basic schooling	
Basic schooling, 9 years (%)	100 (4.4)
Basic schooling, 10 years (%)	198 (8.7)
Basic schooling, 12 years or more (%)	1751 (76.6)
Other schooling	235 (10.3)
Partner, basic schooling	
Basic schooling, 9 years (%)	230 (10.1)
Basic schooling, 10 years (%)	428 (18.8)
Basic schooling, 12 years or more (%)	1317 (57.8)
Other schooling (%)	302 (13.3)
Additional education	
None or missing	342 (14.9)
Skilled worker	283 (12.4)
Short (<3 years)	412 (18.0)
Medium (3–4 years)	751 (32.8)
Long (>4 years)	500 (21.9)
Household income per month	
DKK <12 500 (%)	50 (2.2)
DKK 12 500–24 999 (%)	228 (10.0)
DKK 25 000–39 999 (%)	521 (22.8)
DKK 40 000–65 000 (%)	973 (42.5)
DKK >65 000 (%)	335 (14.6)
Refused or missing (%)	181 (7.9)

Table 2 Fertility related baseline characteristics of enrolled women

Characteristic	$N = 2288$ (%)
Months trying to conceive	
0–2 months	1285 (56.2)
3–4 months	355 (15.5)
5–6 months	259 (11.3)
7–12 months	388 (17.0)
Parity (live births)	
None	1499 (65.5)
One	592 (25.9)
Two	162 (7.1)
Three or more	35 (1.5)
Frequency of sexual intercourse	
⩽3 times per month	373 (16.4)
1 time per week	427 (18.7)
2–3 times per week	1076 (47.2)
4–6 times per week	348 (15.3)
Daily	57 (2.5)
Last type of contraception used	
Missing	83 (3.6)
Birth control pill	1273 (55.6)
Other hormone contraception	63 (2.7)
Ordinary coil	109 (4.8)
Condom	447 (19.5)
Withdrawal	166 (7.3)
Rhythm/safe method	49 (2.1)
Other	98 (4.3)
Brands of birth control pill used	
Never used	101 (4.4)
1 Brand	716 (31.3)
2 Brands	877 (38.3)
3 Brands	388 (17.0)
⩾4 Brands	206 (9.0)

45% drank at the most three drinks per week. Approximately one-third (31%) of the participants were overweight or obese (BMI $\geqslant$25), whereas 47% of their partners were overweight or obese. The great majority (84%) of the women engaged in moderate physical activity for more than 1 h/week and 38% were vigorously active for more than 1 h/week.

What are the main strengths and weaknesses?

In terms of feasibility, Denmark is well suited for this Internet-based cohort study because it has one of the highest prevalence's of Internet access in the world,[31] and because it offers the prospect of linking information collected from cohort volunteers to registry data relating to other exposures and outcomes. Scientifically, the major strength of this cohort of reproductive age women is that exposure data are being collected before conception, thereby avoiding possible selection biases and differential exposure misclassification.

The number of subjects lost to follow-up is always a major concern in cohort studies.[32] In this study, however, we will be able to obtain nearly complete follow-up for the main outcomes, TTP, birthweight, gestational age and miscarriages from nationwide registries. Nevertheless, we will not be able to capture early miscarriages that are not recognized because such miscarriages do not lead to treatment in a hospital setting.

We are collecting data on a wide range of exposures, enabling us to control for many potential confounders in multivariable analyses. We have found few self-reported data items missing and we will be able to compare some of the self-reported data with register data as a validation. Recruiting volunteers through the Internet may raise concerns in the minds of some critics, because the demographics of those with ready Internet access differs from those without it, and among those with Internet access, those who choose to volunteer for studies may differ in lifestyle and health from those who decline. Volunteering to be studied via the Internet does not, however, introduce concerns about validity beyond those already present in other studies using volunteers. Differences between study participants and non-participants do not affect the validity of internal comparisons within a cohort study of volunteers, which is the main concern. Given internal validity, the only problems with studying Internet users would occur if the biologic relations that we are studying differed between Internet users and non-users, a possibility that seems unlikely.

Research plans

In the period 2009–14, we plan to expand the cohort by enroling an additional 10 000 women and their male partners in order to assess male and female risk factors for subfecundity simultaneously.

Can I get hold of the data? Where can I find out more about the study?

The data are held by the Snart-Gravid research teams at the Department of Clinical Epidemiology, Aarhus University Hospital and the Department of Epidemiology, Boston University School of Public Health. Further information about the study and contact information can be obtained from the study website www.snart-gravid.dk. The study is still in progress and access to the data is not yet freely available, but specific proposals for collaborations are welcome.

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References

[1] Olsen J, Melbye M, Olsen SF *et al*. The Danish national birth cohort-its background, structure and aim. *Scand J Public Health* 2001;**29:**300–7.

[2] Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian mother and child cohort study (MoBa). *Int J Epidemiol* 2006;**35:** 1146–50.

[3] Olsen SF, Mikkelsen TB, Knudsen VK *et al*. Data collected on maternal dietary exposures in the Danish national birth cohort. *Paediatr Perinat Epidemiol* 2007;**21:**76–86.

[4] Carlsen E, Giwercman A, Keiding N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *Br Med J* 1992;**305:**609–13.

[5] Jensen TK, Sobotka T, Hansen MA *et al*. Declining trends in conception rates in recent birth cohorts of native Danish women: a possible role of deteriorating male reproductive health. *Int J Androl* 2008;**31:**81–92.

[6] Jorgensen N, Andersen AG, Eustache F *et al*. Regional differences in semen quality in Europe. *Hum Reprod* 2001;**16:**1012–19.

[7] Juul S, Karmaus W, Olsen J. Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. The European infertility and subfecundity study group. *Hum Reprod* 1999;**14:**1250–54.

[8] Nielsen GL, Sorensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. *Br Med J* 2001;**322:**266–70.

[9] Skakkebaek NE, Jorgensen N, Main KM *et al*. Is human fecundity declining? *Int J Androl* 2006;**29:**2–11.

[10] Balen AH, Rutherford AJ. Management of infertility. *Br Med J* 2007;**335:**608–11.

[11] Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. *Obstet Gynecol* 2004;**103:** 51–56.

[12] Bolumar F, Olsen J, Boldsen J. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. The European study group on infertility and subfecundity. *Am J Epidemiol* 1996;**143:**578–87.

[13] Bolumar F, Olsen J, Rebagliato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European study group on infertility subfecundity. *Am J Epidemiol* 1997;**145:**324–34.

[14] Bracken MB, Hellenbrand KG, Holford TR. Conception delay after oral contraceptive use: the effect of estrogen dose. *Fertil Steril* 1990;**53:**21–27.

[15] Juhl M, Olsen J, Andersen AM, Gronbaek M. Intake of wine, beer and spirits and waiting time to pregnancy. *Hum Reprod* 2003;**18:**1967–71.

[16] Zaadstra BM, Seidell JC, Van Noord PA *et al*. Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *Br Med J* 1993;**306:** 484–87.

[17] Bonde JP, Hjollund NH, Jensen TK *et al*. A follow-up study of environmental and biologic determinants of fertility among 430 Danish first-pregnancy planners: design and methods. *Reprod Toxicol* 1998;**12:**19–27.

[18] Jensen TK, Hjollund NH, Henriksen TB *et al*. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. *Br Med J* 1998;**317:**505–10.

[19] Olesen C, Steffensen FH, Nielsen GL, de Jong-van den Berg, Olsen J, Sorensen HT. Drug use in first pregnancy and lactation: a population-based survey among Danish women. The EUROMAP group. *Eur J Clin Pharmacol* 1999;**55:**139–44.

[20] Zaadstra BM, Looman CW, te Velde ER, Habbema JD, Karbaat J. Moderate drinking: no impact on female fecundity. *Fertil Steril* 1994;**62:**948–54.

[21] Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. *Am J Epidemiol* 1997; **146:**32–41.

[22] Jensen TK, Henriksen TB, Hjollund NH *et al*. Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. *Reprod Toxicol* 1998;**12:**289–95.

[23] Hull MG, North K, Taylor H, Farrow A, Ford WC. Delayed conception and active and passive smoking. The Avon longitudinal study of pregnancy and childhood study team. *Fertil Steril* 2000;**74:**725–33.

[24] Weinberg CR, Baird DD, Wilcox AJ. Sources of bias in studies of time to pregnancy. *Stat Med* 1994;**13:** 671–81.

[25] Li DK, Liu L, Odouli R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. *Br Med J* 2003;**327:**368.

[26] Mucci LA, Lagiou P, Hsieh CC *et al*. A prospective study of pregravid oral contraceptive use in relation to fetal growth. *BJOG* 2004;**111:**989–95.

[27] Kristensen J, Langhoff-Roos J, Skovgaard LT, Kristensen FB. Validation of the Danish birth registration. *J Clin Epidemiol* 1996;**49:**893–97.

[28] Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish national hospital register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;**46:**263–68.

[29] Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000;**287:**2398–99.

[30] Rothman KJ, Mikkelsen EM, Sørensen HT, Wise LA, Riis A, Hatch EE. Randomized trial of the effect of questionnaire length on enrollment and missing data in a web-based cohort study. *Epidemiology*. in press.

[31] The Free Encyclopedia. Available at: http://en.wikipedia.org/wiki/List_of_countries_by_broadband_users. (Accessed May 5, 2008).

[32] Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3 edn. Philadelphia, USA: Lippincott Williams & Wilkins, 2008.