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BODY MASS INDEX AND TIME TO
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Body Mass Index and Time to Pregnancy in European Women of childbearing age

By

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ABSTRACT

Body Mass Index and Time to Pregnancy in European Women of childbearing age

By

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Analysis of a pregnancy-based, cross-sectional study was performed to assess the relationship between body mass index (BMI), its covariates, and fecundity as measured by time to pregnancy (TTP). This study suggests fecundity is highest within an ideal range of body composition. Membership in an ideal range of BMI can be predicted for the study population by the year at which menses began, the year at which women began having intercourse without doing anything to avoid pregnancy, and the number of cigarettes smoked at the starting time, defined as the time at which a couple began having sexual intercourse without doing anything to avoid pregnancy. Cigarette smoking, previous gynecological operations, and early age at starting time significantly reduce fecundity as measured by time to pregnancy. Path analysis suggests that the effects of age at starting time, level of completed education, and alcohol consumption at the starting time on time to pregnancy are mediated by body mass index in women with a body mass index greater than 18 kg/m^2.

To Mom and Dad

"For I know the plans I have for you, declares the LORD, plans for welfare and not for evil, to give you a future and a hope."

Jeremiah 29:11

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LIST OF ABBREVIATIONS

ALC ..... Alcohol

BMI ..... Body Mass Index

CI ..... Confidence Interval

ESIS ..... European Studies of Infertility and Subfecundity

FOP ..... First and Only Pregnancy

FR ..... Fecundability Ratio

GYN. OP. ..... Gynecological Operations

LogTTP ..... Time to Pregnancy, log-transformed

NPLB ..... No Prior Live Births

OR ..... Odds Ratio

PID ..... Pelvic Inflammatory Disease

ST ..... Starting Time

STD ..... Sexually Transmitted Disease

TTP ..... Time to Pregnancy

INTRODUCTION

Worldwide variations in fertility, reproductive *behavior* defined by the number of childbirths, and fecundity, the biological *ability* to give birth or achieve a recognized pregnancy (Juul et al., 1999) are increasingly becoming areas of interest to biologists, gynecologists, epidemiologists, and population demographers. As advances in reproduction biology and technology (e.g. in vitro fertilization) simultaneously occur in an era of concern about worldwide population growth, fertility problems are a great public health issue considering its medical, social, and demographic implications. Epidemiology is especially well-suited for fertility (and infertility) research through critically reviewing previous studies, examining the role of medical and behavioral risk factors, and evaluating new therapies and prevention programs (Thonneau and Spira, 1990). In this investigation, data from a pregnancy-based, cross-sectional study of European women was analyzed to investigate the role of body mass index (BMI) and other correlates as they relate to time to pregnancy (TTP), a measure of fecundity.

Chapter 1

BACKGROUND

Current issues in fertility and fecundity research

Previous and current research has investigated the effects on fertility and fecundity of: physical activity and obesity (Norman, 1998; Bongain, 1998), cigarette smoking (Suonio, 1990; Bolumar et al., 1996), caffeine intake (Grodstein et al., 1993b; Bolumar et al., 1997), alcohol consumption (Grodstein et al., 1994; Olsen et al., 1983), diabetes (Yeshaya et al., 1995; Pedersen et al., 1994; Gabbe et al., 1993; Charles et al., 1994), age at onset of menses (Yeshaya et al., 1995; Helm et al., 1995; Otor et al., 1998; Rockhill et al., 1998), and history of gynecological conditions such as sexually transmitted diseases, pelvic inflammatory disease, and endometriosis (Grodstein et al., 1993a; Rodriguez-Escudero et al., 1988; Westrom, 1994; Cates et al.,1994; Berube et al., 1998), to name a few. In addition to the effects of these individual factors, interrelationships and interactions exist between them and study designs vary (e.g. cross-sectional, longitudinal, and case-control), thereby complicating the interpretation of results.

A lively area of debate has centered on the role of maternal nutrition in reproduction. While less disagreement exists over the effects of severe malnutrition, due to famine or conditions such as anorexia nervosa, there is substantial disagreement between physiologists and demographers on the role of mild to moderate undernutrition in fertility (Wood, 1994). The percentage of fat in

the mature human female, as a measure of nutrition, has been argued as playing a causative role in reproductive ability (Frisch 1980; Frisch 1990, Rich-Edwards et al., 1994). Rose Frisch and colleagues have suggested and long maintained that a critical percentage of body fat may be necessary for the onset and maintenance of reproductive ability (menses) in females. This critical weight (fat) hypothesis suggests that the onset of menses at puberty (menarche) occurs at a body composition of about 17% fat. If secondary amenorrhea occurs, for example in women athletes who train heavily, a fat content of about 22% of body weight is required for the resumption and maintenance of menstrual cycles (Frisch 1980; Frisch 1990). From a biological standpoint, this theory argues that the ratio of fat-to-lean body mass is directly related to the endocrine changes of puberty and reproduction since adipose tissue is seen as an extragonadal source of estrogens, a source of estrogen over and above that produced by the gonads (Frisch 1980).

Others investigators, however, have suggested that influences of central nervous system maturation or genetics may play a role (Scott and Johnson, 1982; Kaprio et al., 1995). Kaprio et al. (1995) studied Finnish twins from consecutive birth cohorts to study the variability of body weight and age at menarche due to genetic influences. Age at menarche was compared for 468 monozygotic girls, 378 girls from like-sex dizygotic pairs, 434 girls from opposite-sex pairs, and 141 older female siblings of the twins. The age at menarche was significantly higher for girls from opposite-sex pairs versus like-sex pairs.

Bivariate twin analysis of BMI and age at menarche suggested a high degree of genetic influence (Kaprio et al., 1995).

Less debatable are the effects of behaviors such as cigarette smoking, caffeine, and alcohol consumption. In a sample of pregnant European women, Bolumar et al. (1996) found an association between female smoking (≥ 11 cigarettes per day) and subfecundity, defined as more than 9.5 months of unprotected intercourse until conception (odds ratio (OR) = 1.7, 95% Confidence Interval (CI) 1.3-2.3). Women who smoked were also more likely to consume greater amounts of coffee and alcoholic beverages. Using a similar population-based sample of European women, Bolumar et al. (1997) found a significantly increased OR of 1.45 (95% CI 1.03-2.04) for subfecundity (more than 9.5 months of unprotected intercourse until conception) in the first pregnancy of women who drank more than 500 mg of caffeine per day. This effect was stronger for smokers (OR = 1.56, 95% CI 0.92-2.63) than for non-smokers (OR = 1.38, 95% CI 0.85-2.23). In another study of TTP and smoking in 2198 mothers interviewed at the 20th week of pregnancy, Suonio et al. (1990) found that the longer the conception delay, the more influential the effect of even light smoking. The effect of smoking on conception delay seemed to be dose-dependent.

Sexually transmitted disease-associated genital infections are known to be capable of causing permanent damage to the reproductive tracts of both men and women (Westrom, 1994; Cates et al. 1994). A strong association exists between sexually transmitted diseases (e.g. infection, pelvic inflammatory disease (PID)), and infertility, primarily tubal infertility (Cates et al., 1994).

Experts agree that post-infection infertility is diagnosed more often in women than in men (Westrom, 1994). Reproductive events were studied in a cohort of 1309 pregnancy-seeking women 35 years of age or younger after acute salpingitis and in 451 controls. Salpingitis refers to cases of visually or histopathologically confirmed inflammation of the fallopian tubes (Holmes, 1998). Among these women tubal factor infertility was diagnosed in 12.1% of the case patients versus 0.9% of the controls. Ectopic pregnancy was also more common in the case group. Variables of independent importance for infertility in this study also included the number and severity of infections (Westrom, 1994).

Pelvic inflammatory disease refers to an ascending infection of the endometrium and/or fallopian tubes (Holmes, 1998). The post-infectious scarring of the PID healing process can result in infertility when bilateral tubal adhesions prevent the movement of sperm and/or ova by either damaging the mucosa and cilia of the female reproductive tract or by blocking the fallopian tubes. Occlusion of the fallopian tubes is commonly associated with prior chlamydial infection (Cates et al., 1994). Endometriosis, the presence of functional endometrial tissue outside the uterus, has also traditionally been associated with infertility and is assumed to lower pregnancy rates with increasing severity of disease. Research in women with mild-to-minimal endometriosis, however, suggests that fecundity is not significantly reduced in these women (Berube et al., 1998; Rodriguez-Escudero et al., 1988).

The preceding introduction briefly introduces some of the issues in the field of reproductive epidemiology and demonstrates that the etiology of infertility

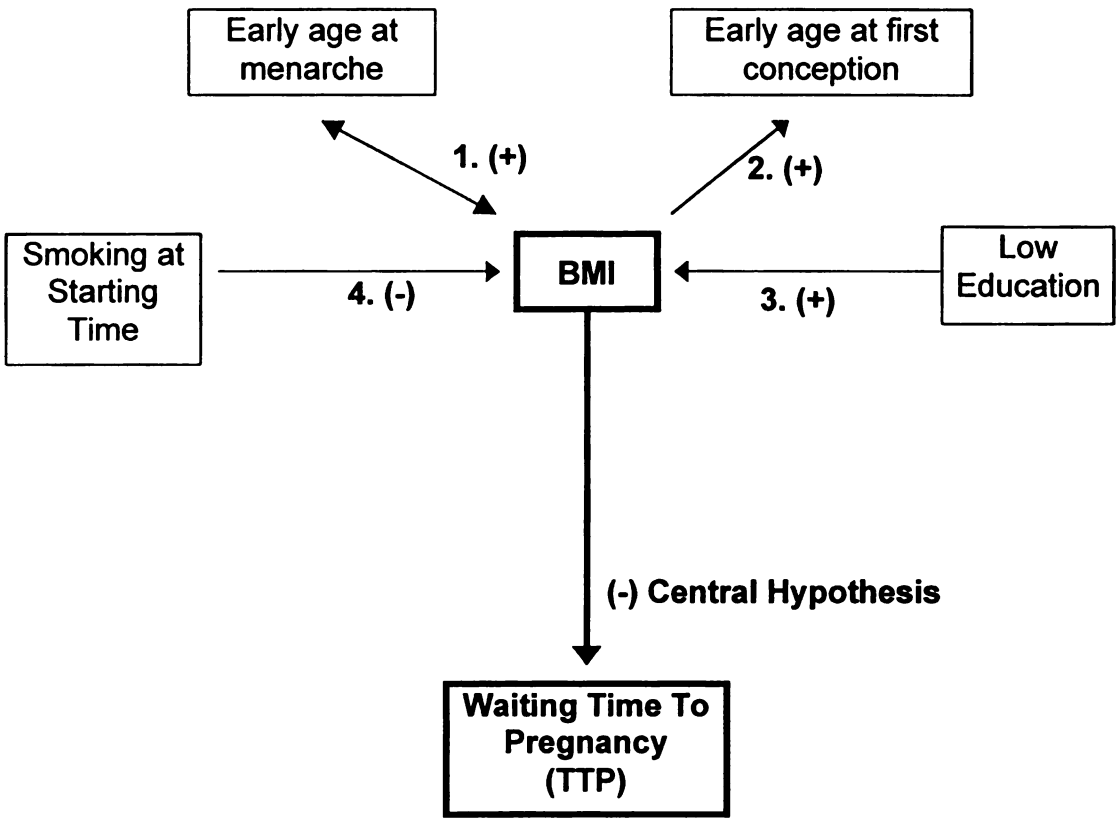
and sub-fecundity and the interactions of its causes are extremely complex. Considering the above debate surrounding the role of BMI in fertility and fecundity, the objective of this thesis is to further investigate the web of causation for covariates explaining both body mass index and time to pregnancy in a sample of European women of childbearing age (Figure 1). Further, the roles of other conditions and behaviors (e.g. smoking, clinical history, etc.) were investigated as they relate to TTP: do they exert their influence through BMI or independent of it? The **central hypothesis** is that *women with a higher BMI before their first and only pregnancy have a decreased waiting time to pregnancy.* Additionally, the following **sub-hypotheses** were examined:

1. increased adult BMI is positively associated with early age at menarche;
2. increased adult BMI is positively associated with early age at first conception;
3. low level of education is positively associated with increased BMI;
4. maternal smoking is negatively associated with increased BMI.

European Studies of Infertility and Subfecundity (ESIS)

In 1990 a European study group was formed (ESIS, European Studies of Infertility and Subfecundity) to conduct comparable studies of fertility and fecundity in European countries. A cross-sectional, pregnancy-based survey of women from Denmark, Germany, Italy, Sweden, and France was conducted by ESIS in 1992. Women were approached immediately following delivery at a

hospital or birth clinic or at an antenatal care visit after 20 weeks gestation. The institutions were chosen because they served geographically well-defined populations. All pregnant women during a defined data collection period were invited to participate. The participating women were asked to complete a highly-structured questionnaire that covered such areas as health and education, reproductive history, and pregnancy planning (Juul et al., 1999).



*(+) denotes positive association
(-) denotes negative association

FIGURE 1: Hypothesized causation web for covariates explaining Body Mass Index (BMI) and Time to Pregnancy (TTP).

Chapter 2

METHODS

The study population

The study was structured as a pregnancy-based, cross-sectional survey—all women who were recruited to participate were either currently pregnant or very recently pregnant. Women were recruited from the countries of Denmark, France, Germany, Italy, and Sweden in 1992. The 4035 participants in the initial sample with information on time to pregnancy were grouped into three populations based on their pregnancy history. The first group (1340) included women for whom this pregnancy was the first and only pregnancy (FOP); the second group (417) included women with no prior live births (NPLB); the third group included all others (2278). Time to pregnancy (TTP, months), the amount of time it took for conception to occur was determined as a continuous variable; body mass index (BMI, kg/m^2), also continuous, was obtained by dividing an individual's weight (kg) by the square of their height (m).

Questionnaire

A highly structured questionnaire (Appendix A) was administered to pregnant or recently pregnant women at an antenatal care visit after 20 weeks gestation or at a hospital or birth clinic following delivery. The format of the questionnaire was structured by reproductive experience: the groups of questions asked depended on whether or not the pregnancy was the woman's

first, pregnancy and the circumstances of conception (e.g. never used birth control; result of birth control failure; intentionally discontinued birth control), and/or menstrual status at conception (menses had returned since the previous pregnancy, menses had *not* returned since the previous pregnancy).

The content of the questionnaire covered such areas as health and education, reproductive history, starting time and waiting time to pregnancy (TTP) for the current or most recent pregnancy, exposures around the starting time, and pregnancy planning. "Starting Time" was defined as the time at which a couple began having sexual intercourse *without doing anything to avoid pregnancy.* In particular, questions were asked about the woman's age at onset of menses, her height and weight at starting time, age at starting time, and completed level of education. Questions were also asked about: the woman's clinical history (past presence of pelvic inflammatory disease; infection with chlamydia, gonorrhea, or another sexually transmitted disease; the presence of fibroids or myomas/endometriosis; past curettage or other operations of the uterus, tubes, or ovaries; oral contraceptive use; and diabetes) and exposures at or near the starting time (smoking status: cigarettes, cigars, and/or pipes; alcohol consumption; beer, wine, liquor; and caffeine: coffee, tea, cola). The exact questions are included in Appendix A (page 55). TTP was defined as the length of time from the "Starting Time" until conception. This question was phrased "How long was it from that 'starting time' until you became pregnant? (the date you became pregnant is the date you conceived)" (Appendix A). Women could respond in terms of weeks, months, and/or years.

The questionnaire was designed for self-administration. In two Italian centers, however, it was administered by female interviewers but there were no marked differences attributable to administration style (Juul et al. 1999).

Statistical Analysis

Figure 2 is a step-by-step flowchart of the methods used in this investigation. Univariate analyses were performed and the median and geometric mean of TTP, BMI, age at menarche (in years), and age at starting time (in years) were compared for the three groups of women (Figure 2, step 1). The Kruskal-Wallis test for non-parametric distributions was used to calculate the significance of differences in the medians. Spearman rank correlations and

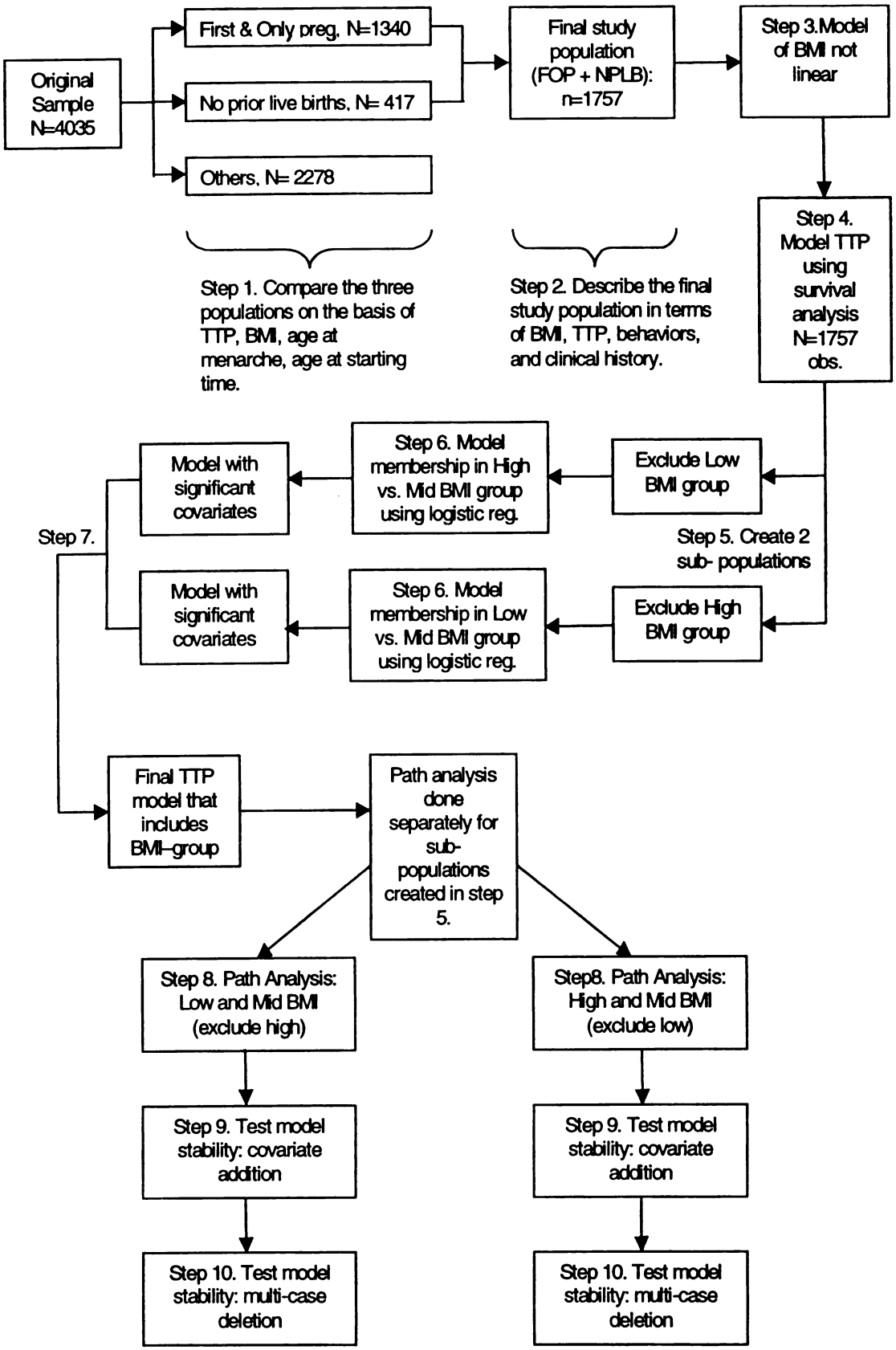


Figure 2: Flowchart of analytical methods

partial Spearman correlations were used to examine correlations between covariates.

Univariate analysis and the Kruskal-Wallis test was used to describe the final study population (n = 1757) (Figure 2, step 2) stratified by age at menarche (grouped into three categories: <10, 11-14, ≥15 years), age at starting time (grouped into six categories: ≤20, 21-25, 26-30, 31-35, 36-40, and ≥41 years old), BMI (grouped into four categories: <18, 18-25, 25-30, and ≥30 kg/m^2), and levels of completed education (leaving school at or before the age of 15, between the ages of 16 and 17, at age 18 or older, completed manual trade training, professional training, a university degree, and other). Previous analysis of this data reported regional differences in time to pregnancy. Therefore, nationality was examined as a possible confounder of the relationship between BMI and TTP.

After establishing the final study population, linear regression (PROC GLM in SAS) was employed to model BMI as a continuous variable with age at menarche, age at starting time, smoking status at starting time, and level of completed education as covariates (Figure 2, step 3).

Survival analysis, utilizing proportional hazards regression (PROC PHREG in SAS), was employed to model TTP, in months, as a continuous outcome variable (Figure 2, step 4). There is no censoring of TTP in this sample of women because of the pregnancy-based structure of the study—all women conceived and therefore had the event. In the proportional hazards regression, the TIES=EXACT method was used instead of the Breslow method to break ties.

The Breslow method produces estimates in breaking ties that occur when two or more individuals have the same data points. The EXACT method does not utilize estimates (SAS, 1999). The hazard ratio in the output of proportional hazards regression represents the Fecundability Ratio (FR). Fecundability is defined as the monthly probability of conception: a value less than one represents decreased fecundability; a value greater than one represents increased fecundity. Confounders were determined by sequentially removing covariates and noting the effect of their removal on the BMI FRs. A covariate was retained in the model if its removal resulted in at least a 10% change in any of the BMI fecundability ratios.

The final sample of women (n = 1757) was split into two sub-populations based on the categorical grouping of BMI: one group excluded the highest BMI category ($\geq$30 kg/m^2), the other excluded the lowest BMI category ($<$18kg/m^2) (Figure 2, step 5). Logistic regression was used to model membership in the extreme BMI categories within the sub-populations (Figure 2, step 6). Confounders were assessed by sequentially dropping covariates from a starting model and comparing the reduced model to the starting model by means of a Chi-square test with degrees of freedom = ($df_{\text{starting model}} - df_{\text{reduced model}}$); alpha = .05. Covariates that were significant in the Chi-square test were retained in the model.

Those covariates that were significant ($p < 0.05$) in the BMI-group membership logistic models were entered into the TTP survival analysis model from step 4 to produce a final TTP survival analysis model (Figure 2, step 7).

The PROC CALIS (Covariance Analysis of Linear Structural equations) procedure in SAS was used for path analysis to model multiple linear paths with BMI and TTP (log-transformed) as continuous endogenous variables (Figure 2, step 8). The CALIS procedure has the advantage of being able to model intervening effects in the regression; proportional hazards regression does not permit this. For the purpose of path analysis, age at starting time in years, age at menarche in years, smoking (the number of cigarettes smoked per day) and alcohol consumption (the number of alcoholic beverages consumed per week) at starting time were continuous covariates; level of completed education was replaced by Blom-transformed ranks. Gynecological operations included past curettage or other operations of the uterus, tubes, or ovaries (Methods, questionnaire, page 9). The following linear structural equations were used in parallel invocations of the CALIS procedure:

$$\textbf{BMI} = \beta_1(\text{age at starting time}) + \beta_2(\text{age at menarche}) + \beta_3(\text{Cigarettes}) + \beta_4(\text{Alcohol}) + \beta_5(\text{Education level}) + \varepsilon_{BMI}$$

$$\text{LogTTP} = \beta_6(\text{age at starting time}) + \beta_7(\text{age at menarche}) + \beta_8(\text{Cigarettes}) + \beta_9(\text{Alcohol}) + \beta_{10}(\text{Education level}) + \beta_{11}(\text{any gynecological operations}) + \beta_{12}\textbf{BMI} + \varepsilon_{LogTTP}$$

One-sided t-tests were used to calculated the significance level of regression coefficients produced by the CALIS procedure.

The stability of the models produced by path analysis was tested by two methods. First, the models were re-constructed by adding one covariate at a time and noting the influence of its addition on the other β-coefficients (Figure 2, step 9). Variables which, upon addition to the model, changed β-coefficients by 20% or more indicated an unstable model or possible confounding. Secondly, covariate addition was repeated after multi-case deletion to assess the influence of outliers on model stability (Figure 2, step 10).

All analyses were performed using the SAS statistical package, version 8.0.

Chapter 3

RESULTS

Selection and description of the study population

Table 1 describes women for whom the pregnancy was their first and only (FOP) and women who had no prior live births (NPLB) in terms of time to pregnancy, body mass index, age at menarche, and age at starting time (Figure 2, step 1). The significance of differences in the medians of the primary predictor variables (age at menarche, age at starting time, smoking at starting time, level of completed education) were tested using the Kruskal-Wallis test. The FOP and NPLB populations did not differ in the median of TTP (p=.0951), BMI (p=.8105), or age at menarche (p=.7623). They did differ, however, in the median age at starting time (FOP = 25 years, NPLB = 26 years, $p < 0.0001$). The FOP and NPLB populations were combined, excluding pregnancies that were the result of contraceptive failures (n=236 for the FOP population), yielding a final study population of 1757 women with information on time to pregnancy who had no prior live births or for whom this pregnancy was their first and only pregnancy.

Tables 2-4 describe the final study population (n = 1757) (Figure 2, step 2). The median of BMI was statistically significantly different when stratified by age at menarche (p<.0001), age at starting time (p=.0184), completed level of education (p=.0073), and nationality (p=.0011) (Table 2). BMI was highest for those women in the youngest grouping of age at menarche and it decreased with increasing age at menarche. BMI tended to increase with older age at starting

Table 1: Description of Study Populations

TTP (months) stratified by Population

Population	n	median	geometric mean	5%	95%
First and only pregnancy	1340	3	3.38	0.5	36
No prior live births	417	3	4.11	0.2	60
total	3438				

BMI (Kg/m^2) stratified by Population

Population	n	median	geometric mean	5%	95%
First and only pregnancy	1317	21.26	21.63	17.99	28.08
No prior live births	411	21.26	21.72	17.91	28.73
total	3952				

Age at Menarche (years) stratified by Population

Population	n	median	geometric mean	5%	95%
First and only pregnancy	1253	13	12.88	11	15
No prior live births	397	13	12.86	11	15
total	3776				

Age at Starting time (years) stratified by Population

Population	n	median	geometric mean	5%	95%
First and only pregnancy	1322	25*	25	19	32
No prior live births	409	26*	26	19	36
total	3406				

*p-value (difference in medians) <.0001

TABLE 2: BMI stratified by Primary Predictor Variables—FOP / NPLB

	N	MED	5%	95%	Kruskal-Wallis
Age at menarche					
≤10	151	21.95	18.52	28.42	
11-14	1376	21.30	18.07	28.39	
≥15	201	20.57	17.37	25.35	***p<0.0001***
Age at starting time					
≤20	227	20.94	17.36	29.67	
21-25	685	21.30	17.91	28.39	
26-30	605	21.33	18.07	27.74	
31-35	171	21.08	18.69	27.43	
36-40	37	21.48	19.37	25.82	
≥41	3	28.40	26.85	29.88	***p=0.0184***
Completed education					
left < 15	176	21.64	17.58	30.10	
left 16-17	139	21.14	17.47	31.05	
left 18+	350	21.48	18.07	26.30	
manual trade	197	21.83	18.08	28.39	
prof train.	466	21.08	17.93	28.03	
univ. degree	320	20.82	18.03	26.97	
other	37	21.22	17.63	27.44	
no answer	33	21.50	18.78	31.14	
missing	10	20.90	18.73	27.68	***p=0.0073***
Country					
Denmark	216	21.76	18.25	29.38	
Germany	570	21.20	17.51	29.38	
Sweden	317	21.48	18.67	27.51	
N Italy	184	21.09	17.75	26.57	
S Italy	210	21.26	17.67	28.52	
France	231	20.70	17.91	26.56	***p=0.0011***
Smoking at starting time					
yes	608	21.17	17.58	29.38	
no	1115	21.30	18.08	27.77	
no answer	5	22.03	18.37	24.49	*p=0.2631*

TABLE 3: TTP stratified by Primary Predictor Variables—FOP / NPLB

	N	MED	5%	95%	Kruskal-Wallis
Smoking at starting time					
yes	618	4.00	0.50	48.00	
no	1133	3.00	0.50	36.00	
no answer	6	1.25	0.00	8.00	***p<0.0001***
BMI group					
<18	125	4.00	0.50	42.00	
18-24	1410	3.00	0.30	39.00	
25-29	169	3.00	0.50	36.00	
≥30	53	4.00	0.50	83.00	*p=0.0635*
Completed Education					
left <15	176	3.00	0.50	48.00	
left 16-17	144	4.00	0.50	52.00	
left 18+	354	3.00	0.50	38.00	
manual trade	205	3.00	0.20	36.00	
prof training	469	4.00	0.50	42.00	
univ. deg.	322	2.20	0.20	31.00	
other	39	3.00	0.50	54.00	
no answer	37	3.00	0.00	60.00	
missing	11	2.00	0.20	120.00	***p<0.0001***
Age at menarche					
≤10	160	3.00	0.25	35.00	
11-14	1393	3.00	0.50	45.00	
≥15	204	3.00	0.50	36.00	*p=0.9524*
Age at starting time					
≤20	238	5.00	0.30	84.00	
21-25	698	3.00	0.50	42.00	
26-30	610	3.00	0.50	36.00	
31-35	171	3.00	0.50	28.00	
36-40	37	2.50	0.00	27.00	
≥41	3	1.40	1.00	32.00	***p=0.0002***

TABLE 4: TTP stratified by Clinical/Medical History variables—FOP / NPLB

	N	MED	5%	95%	Kruskal-Wallis
PID					
no	1602	3.00	0.50	36.00	
yes	151	5.00	0.50	81.00	***p=0.0003***
Chlamydia					
no	1635	3.00	0.50	42.00	
yes	118	3.00	0.20	33.00	*p=0.5746*
Gonorrhea					
no	1722	3.00	0.50	39.00	
yes	31	5.00	0.20	96.00	***p=0.0205***
Other STD					
no	1623	3.00	0.50	39.00	
yes	130	3.00	0.30	48.00	*p=0.5297*
Ovarian Cyst					
no	1620	3.00	0.40	36.00	
yes	132	5.00	0.50	96.00	***p<0.0001***
Fibroids/myomas					
no	1715	3.00	0.50	42.00	
yes	38	4.00	0.20	43.00	*p=0.7105*
Endometriosis					
no	1729	3.00	0.50	36.00	
yes	23	36.00	0.90	96.00	***p<0.0001***
Diabetes					
no	1739	3.00	0.50	42.00	
yes	13	2.00	0.50	12.00	*p=0.2329*
Curettage					
no	1545	3.00	0.50	36.00	
yes	208	3.60	0.20	54.00	*p=0.0543*
Other Gyn. operations					
no	1679	3.00	0.50	36.00	
yes	73	12.00	0.50	96.00	***p<0.0001***
Oral contraceptive use					
no	365	3.00	0.50	72.00	
yes	1379	3.00	0.50	36.00	*p=0.8393*

time. BMI was highest in those women who left school before the age of 15 and in those women with manual trade training; women with a university degree had the lowest BMI. Body mass index was highest for women of Danish nationality and lowest for French women. No statistically significant differences in BMI were detected when stratified by smoking status at starting time (p=.26).

Women who smoked had a significantly increased median TTP (p<.0001) (Table 3). TTP was the longest for women with a BMI at the extremes of the distribution, <18 kg/m^2 and ≥30 kg/m^2, but differences in the medians were not statistically significant (p=.0635). When the middle two groups are combined (BMI = 18-30 kg/m^2) and the significance of differences in medians are again compared, the low BMI group (median TTP = 4 months, 125 observations) emerged as having a significantly longer median TTP than the two middle groups combined (median TTP = 3 months, 1579 observations; p = .024). However, there is no statistically significant difference in median TTP for the high BMI group (median TTP = 3 months, 1579 observations) when compared to the combined middle two groups (median TTP = 4 months, 53 observations; p=.113).

TTP was longer for women who left school between the ages of 16 and 17 and with professional training; women who left school after the age of 18 or with a university degree had the shortest TTP (p<.0001) (Table 3). There were no statistically significant differences in TTP when stratified by age at menarche (p = .95). The median TTP was statistically significantly different for different levels of age at starting time (p = .0002), decreasing with increasing age.

Differences in the median TTP were also calculated for clinical history variables as potential confounders, namely pelvic inflammatory disease (PID), chlamydia, gonorrhea, other STDs, ovarian cysts, fibroids/myomas, endometriosis, curettage, other gynecological operations, diabetes, and oral contraceptive use (Table 4). Time to pregnancy was significantly longer for women with a history of PID ($p=.0003$), gonorrhea ($p=.0205$), ovarian cysts ($p<.0001$), endometriosis ($p<.0001$), and other operations of the uterus, tubes, or ovaries ($p<.0001$).

TTP modeling using survival analysis

Using proportional hazards regression (survival analysis), TTP was modeled using time of conception as the event and both the primary predictor and clinical history variables as covariates (Figure 2, step 4). The hazard ratio in the output corresponds to the fecundability ratio. After confounder assessment, the TTP survival analysis model (Table 5) included, in addition to the BMI dummy variables, all past gynecological operations (past curettage and other operations of the uterus, tubes, or ovaries): likelihood ratio = 41.3662, 4 df, $p<.0001$. Membership in the low BMI group (<18 kg/m^2), in the high BMI group (≥ 30 kg/m^2), and previous gynecological operations all reduced fecundity at the statistically significant level ($p < 0.05$): fecundibility ratio (FR) = 0.820, 0.757, 0.693, respectively.

Table 5: Fecundability ratios in time to pregnancy modeling using proportional hazards regression, TIES=EXACT. Likelihood ratio = 41.3662, 4df, p<0.0001.

Variable	Fecundability Ratio	p	95% C.I.
BMI <18 kg/m^2	0.82	0.0339	(0.683, 0.985)
BMI 18-24 kg/m^2*	1.000	-	-
BMI < 25-29 kg/m^2	1.028	0.7327	(0.876, 1.207)
BMI ≥30 kg/m^2	0.757	0.0476	(0.575, 0.997)
any gynecological operation#	0.693	<0.0001	(0.607, 0.793)

*referent group
#past curettage or other operations of the uterus, tubes, or ovaries

BMI-group membership modeling

As membership in the tails of the BMI distribution was significant in the TTP survival analysis model, logistic regression was used to separately model membership in the low and high BMI categories (Figure 2, steps 5-6). To model membership in the low BMI group (<18 kg/m^2), a population was created that excluded those individuals in the high BMI group (≥30 kg/m^2). Membership in the low BMI group served as the dichotomous outcome in the regression model, using the combined middle two groups (18-30 kg/m^2) as the reference. A starting model, based on 1357 observations, was constructed that included age at interview, age at starting time, age at menarche, number of cigarettes smoked per day at starting time, number of alcoholic beverages consumed per week at starting time, caffeinated coffee consumption (cups per day) at starting time, completed level of education, and presence of maternal diabetes. To test for

confounders, covariates were removed successively from the starting model (Likelihood ratio Chi-square = 51.4046, 12 df, p<.0001). The final predictive model for membership in the low BMI group included age at starting time and age at menarche (Likelihood ratio Chi-square = 41.1788, 2 df) (Table 6a).

The model for membership in the high BMI group, based on 1304 observations, was constructed in a manner identical to that used for the low BMI group, with the middle two groups serving as the reference group (Table 6b). The same initial covariates were included in the starting model (Likelihood ratio Chi-square = 23.0537, 12 df, p=.0273). Only one covariate, number of cigarettes smoked per day at starting time, remained in the final model (Likelihood ratio Chi-square = 10.2468, 1 df, p=0.0014).

Table 6a: Logistic model of membership in the low BMI group (<18kg/m^2) versus the middle BMI groups (18-30 kg/m^2). Likelihood ratio Chi-square = 41.1788, 2 df, p < 0.0001, n = 1357.

Covariate	Estimate	Chi-square	p
age at menarche	0.256	18.169	<.0001
age at starting time	-0.121	22.555	<.0001

Table 6b: Logistic model of membership in the high BMI group (30+kg/m^2) versus the middle BMI groups (18-30 kg/m^2). Likelihood ratio Chi-square = 10.2468, 1 df, p = 0.0014, n = 1304.

Covariate	Estimate	Chi-square	p
number of cigarettes	0.0527	11.959	0.0005

Final TTP survival analysis model

The covariates that were retained in each of the BMI-membership models were re-entered into the TTP proportional hazards model from Table 5, yielding a model that included age at starting time, BMI group, age at menarche, all past gynecological operations, and the number of cigarettes smoked per day at the starting time (Figure 2, step 7) (Table 7). Of the covariates in the model, the following were statistically significant: age at starting time less than 21 years ($p < 0.0001$), age at menarche 10 years or younger ($p = 0.025$), 11-15 cigarettes per day ($p = 0.009$), 16-20 cigarettes per day ($p = 0.0003$), more than 20 cigarettes per day ($p = 0.016$), and any past gynecological operation ($p < 0.0001$). Only age at menarche 10 years or younger was significantly associated with increased fecundability ($FR > 1.0$); all other significant covariates were associated with decreased fecundability ($FR < 1.0$).

Path analysis of BMI and TTP

Figure 3 is a diagrammatic representation of the results of path analysis (Figure 2, step 8) of the effects of the covariates from Table 7 (with the addition of alcohol and education) on BMI and TTP. Path analyses were completed separately for the low BMI group versus the middle two groups and for the high group versus the middle (as in the logistic regression).

The term β_{12}BMI (Methods, page 12) is modeled as a potential intervening variable in predicting LogTTP. Both age at menarche and age at starting time are statistically significant predictors of body mass index in path analysis at the p =

Table 7: Final TTP proportional hazards model, including covariates that were significant predictors of BMI group membership. Likelihood ratio Chi-square = 108.2776, 16 df, p < 0.0001.

Variable	Wald Chi-Square	p	Hazard Ratio	95% C.I.
Age at starting time (yrs)				
<21	25.667	<0.0001	0.651	(0.551, 0.769)
21-25	3.5525	0.060	0.896	(0.800, 1.004)
26-30	-	-	1.000	-
31-35	0.9683	0.325	0.916	(0.768, 1.091)
36-40	0.0975	0.755	0.947	(0.672, 1.334)
>40	2.5236	0.112	3.116	(0.767, 12.665)
BMI (kg/m^2)				
<18	3.1607	0.075	0.833	(0.681, 1.019)
18-25	-	-	1.000	-
25-30	0.3511	0.554	1.052	(0.889, 1.246)
>30	2.7882	0.095	0.781	(0.585, 1.044)
Age at menarche (yrs)				
≤10	5.0548	0.025	1.373	(1.042, 1.811)
11-14	-	-	1.000	-
>14	0.3187	0.572	1.045	(0.897, 1.217)
Cigarettes (number/day)				
0	-	-	1.000	-
1-5	0.0115	0.915	0.985	(0.751, 1.293)
6-10	1.5657	0.211	0.891	(0.744, 1.067)
11-15	6.8798	0.009	0.798	(0.675, 0.945)
16-20	13.2751	0.000	0.662	(0.530, 0.826)
>20	5.8087	0.016	0.793	(0.656, 0.958)
Any past Gync. operation	26.9244	<0.0001	0.690	(0.600, 0.794)

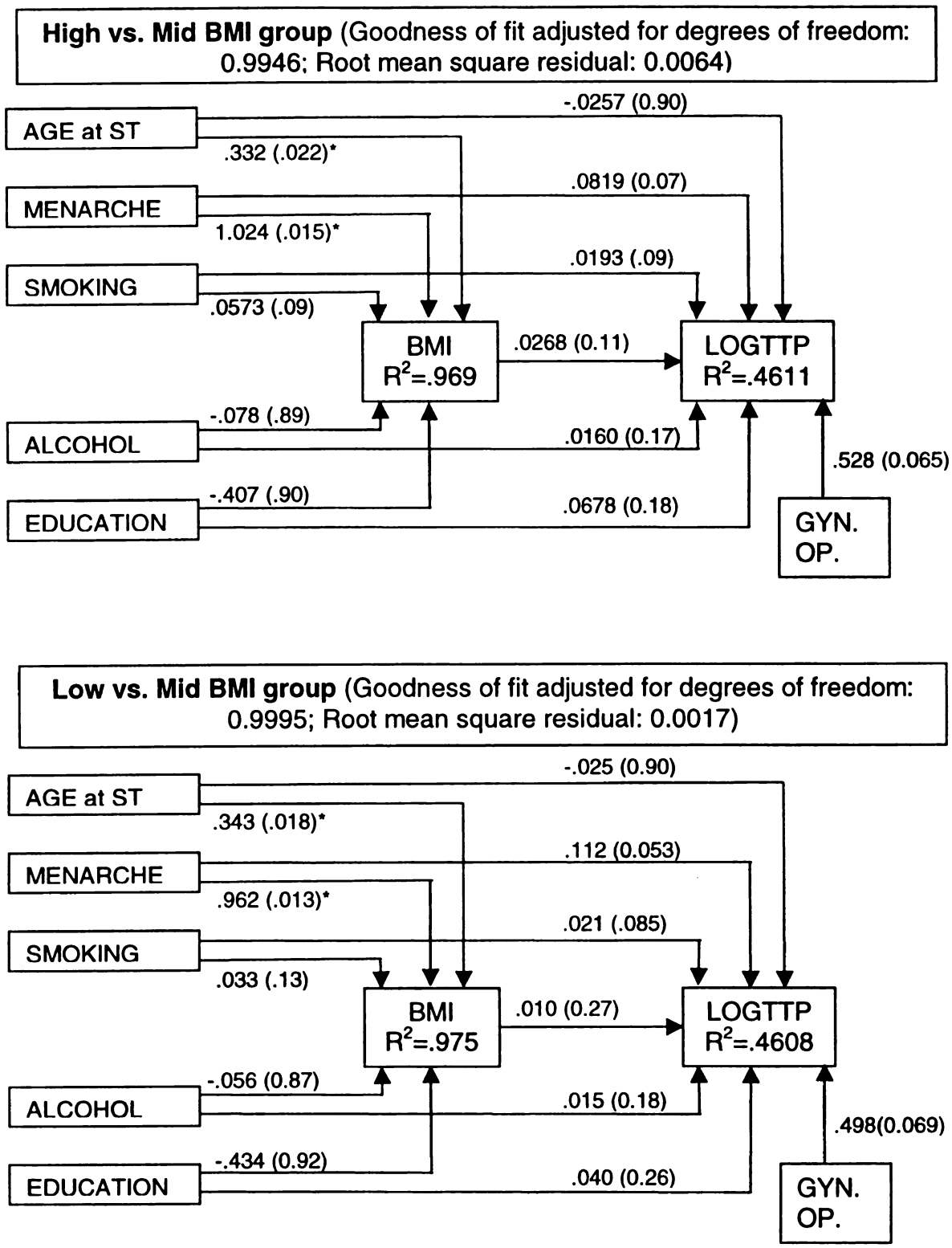


Figure 3: Beta coefficients and p-values (in parentheses) of path analysis using PROC CALIS.

.05 level (Figure 3). There is virtually no effect of BMI on logTTP in the Low vs. Mid model (β=.010) as opposed to the High vs. Mid model (β=.0268). Figure 3 indicates that, for every unit increase (kg/m^2) in body mass index *over 18 kg/m^2* (the High vs. Mid group), time to pregnancy increases e^{β} months. For example, an increase of 1 kg/m^2 in BMI results in an increase in TTP of 1.03 months. Similarly, for women *with a BMI greater than 18 kg/m^2*, every 1-year increase in age at starting time decreases TTP by $e^{-.0257}$ months, or .97 months. These effects are multiplicative; the greater the increase, the greater the effect on TTP. The β-coefficients of all covariates are larger in magnitude in the paths to BMI than to logTTP. With the exception of the influence of BMI on logTTP, path analysis indicates that in the extreme groups (low and high BMI groups), relationships between the predictor variables and BMI and logTTP are similar.

To test the stability of the models obtained in path analysis, the models were re-constructed by adding one covariate at a time to the model and noting the influence of its addition on the β-coefficients (Figure 2, step 9) (Table 8). The addition of age at menarche to the model changed β-coefficients by more than 20% in every model (Table 8a-d) while addition of age at starting time had an effect only in the High vs. Mid BMI path (Table 8c).

Model stability was also tested using multi-case deletion diagnostics (Table 9). Five individuals were temporarily dropped to test if the instability of the models, indicated by the effect of age at menarche, was due to outliers. An age at menarche greater than 18 years qualified as an outlier. The addition of age at menarche still changed the β-coefficients by more than 20% (Table 9, bold).

While addition of the age at menarche term still produced instability in the model, the β-coefficients of all terms in the High vs. Mid BMI group models (Tables 9c and 9d) were virtually unchanged when compared to the coefficients before case deletion (Tables 8c and 8d). This was not true for the Low vs. High BMI group models (Tables 9a and 9b). After case deletion, the β-coefficients were different for age at starting time (increased), age at menarche (decreased), smoking

Table 8: Model stability of path analysis—stepwise covariate addition
a: Low vs. Mid BMI group CALIS Models--BMI as endogenous variable

Variable added	β AGE at ST	βMENARCHE	βSMOKING	βALCOHOL	βEDU
AGE at ST	0.8207	-	-	-	-
MENARCHE	**0.3339**	0.9847	-	-	-
SMOKING	0.3352	0.9713	0.0336	-	-
ALCOHOL	0.3451	0.9652	0.0296	-0.0529	-
EDUCATION	0.3427	0.9631	0.0315	-0.0548	-0.4343
*logTTP	0.3431	0.9624	0.0329	-0.0561	-0.4340

**as endogenous variable*
$R^2 = 0.96$

b: Low vs. Mid BMI group CALIS Models--logTTP as endogenous variable

Variable added	βBMI	βGYN. OP	βSMOKING	β AGE at ST	βMENARCHE	βALC.	βEDU
BMI	0.0539	-	-	-	-	-	-
GYN.OP	0.0504	0.5415	-	-	-	-	-
SMOKING	0.0463	0.4933	0.0238	-	-	-	-
AGE at ST	0.0467	0.4936	0.0238	-0.00034	-	-	-
MENARCHE	**0.0072**	0.4974	0.0217	**-0.0207**	0.1080	-	-
ALCOHOL	0.0085	0.4937	0.0204	-0.0235	0.1090	0.0153	-
EDUCATION	0.0098	0.4978	0.0207	-0.0254	0.1106	0.0151	0.0403

$R^2 = 0.46$

c: High vs. Mid BMI group CALIS Models--BMI as endogenous variable

Variable added	βSMOKING	β AGE at ST	βMENARCHE	βALCOHOL	βEDU
SMOKING	1.3820	-	-	-	-
AGE at ST	**0.1211**	0.8255	-	-	-
MENARCHE	**0.0641**	**0.3059**	1.0710	-	-
ALCOHOL	0.0594	0.3230	1.0510	-0.0676	-
EDUCATION	0.0554	0.3310	1.0257	-0.0766	-0.4084
*logTTP	0.0573	0.3319	1.0239	-0.0783	-0.4069

**as endogenous variable*
$R^2 = 0.97$

d: High vs. Mid BMI group CALIS Models--logTTP as endogenous variable

Variable added	βBMI	βGYN. OP	βSMOKING	β AGE at ST	βMENARCHE	βALC.	βEDU
BMI	0.0528	-	-	-	-	-	-
GYN.OP	0.0491	0.5659	-	-	-	-	-
SMOKING	0.0455	0.5419	0.0214	-	-	-	-
AGE at ST	0.0473	0.5163	0.0213	-0.00152	-	-	-
MENARCHE	**0.0240**	0.5249	0.0201	**-0.0198**	0.0776	-	-
ALCOHOL	0.0254	0.5206	0.0187	-0.0226	0.0785	0.0161	-
EDUCATION	0.0268	0.5281	0.0193	-0.0257	0.0819	0.0160	0.0678

$R^2 = 0.46$

Table 9: Model stability of path analysis—after multi-case deletion
a: Low vs. Mid BMI group CALIS Models--BMI as endogenous variable

Variable added	β AGE at ST	βMENARCHE	βSMOKING	βALCOHOL	βEDU
AGE at ST	0.8657	-	-	-	-
MENARCHE	**0.5856**	0.5569	-	-	-
SMOKING	0.5765	0.5581	0.5222	-	-
ALCOHOL	0.5769	0.5668	0.0471	-0.0502	-
EDUCATION	0.5722	0.5657	0.0589	-0.0795	-0.4047
*logTTP	0.5717	0.5666	0.0602	-0.0803	-0.3835

**as endogenous variable*
$R^2 = 0.98$

b: Low vs. Mid BMI group CALIS Models--logTTP as endogenous variable

Variable added	βBMI	βGYN. OP	βSMOKING	β AGE at ST	βMENARCHE	βALC.	βEDU
BMI	0.0505	-	-	-	-	-	-
GYN.OP	0.0470	0.5693	-	-	-	-	-
SMOKING	0.0435	0.5307	0.0206	-	-	-	-
AGE at ST	0.0374	0.5263	0.0207	-0.00545	-	-	-
MENARCHE	**0.0281**	0.5350	0.0212	**-0.0156**	0.0573	-	-
ALCOHOL	0.0294	0.5361	0.0204	-0.0183	0.0582	0.0157	-
EDUCATION	0.0307	0.5410	0.0208	-0.0207	0.0604	0.016	0.0536

$R^2 = 0.44$

c: High vs. Mid BMI group CALIS Models--BMI as endogenous variable

Variable added	βSMOKING	β AGE at ST	βMENARCHE	βALCOHOL	βEDU
SMOKING	1.382	-	-	-	-
AGE at ST	**0.1211**	0.8255	-	-	-
MENARCHE	**0.0642**	**0.3056**	1.071	-	-
ALCOHOL	0.0595	0.3226	1.052	-0.0673	-
EDUCATION	0.0555	0.3305	1.026	-0.0763	-0.4058
*logTTP	0.0575	0.3314	1.025	-0.0780	-0.4043

**as endogenous variable*
$R^2 = 0.97$

d: High vs. Mid BMI group CALIS Models--logTTP as endogenous variable

Variable added	βBMI	βGYN. OP	βSMOKING	β AGE at ST	βMENARCHE	βALC.	βEDU
BMI	0.0528	-	-	-	-	-	-
GYN.OP	0.0491	0.5528	-	-	-	-	-
SMOKING	0.0455	0.5004	0.0217	-	-	-	-
AGE at ST	0.0471	0.5017	0.0216	-0.00146	-	-	-
MENARCHE	**0.0236**	0.5095	0.0204	**-0.0199**	0.0785	-	-
ALCOHOL	0.0250	0.5049	0.0190	-0.0228	0.0794	0.0165	-
EDUCATION	0.0265	0.5123	0.0195	-0.026	0.0830	0.0164	0.0701

$R^2 = 0.46$

(increased), alcohol (increased), and education (decreased) (Table 9a versus Table 8a). In Table 9b, only the coefficients for BMI (increased), gynecological operations (increased), and age at menarche (decreased) are changed from Table 8a (before case deletion).

Chapter 4

DISCUSSION

The results suggest that fecundity, as measured by time to pregnancy, is highest within an ideal range of body composition (Table 3, Table 5). Membership in the left tail of the BMI distribution (<18 kg/m^2) can be explained by the year at which menses began and the year at which women began having intercourse without doing anything to avoid pregnancy. The number of cigarettes smoked at the starting time predicts membership in the right tail of the distribution (≥30 kg/m^2) (Table 6). Cigarette smoking, previous gynecological operations, and early age at starting time are associated with significantly reduced fecundity (Table 7). The results of path analysis suggest that age at starting time, alcohol consumption at starting time, and completed level of education may exert their influence on time to pregnancy through an intervening effect of body mass index (Figure 3).

The study population

In order to increase sample size and power, the first and only pregnancy (FOP) and no prior live births (NPLB) populations were combined. In so doing, it was assumed that women who have had no prior live births (NPLB) have not carried (due to spontaneous abortion, miscarriage, etc.) their pregnancies long enough to experience the changes in body composition associated with pregnancy (Gunderson and Abrams, 1999). A significant difference was detected

for age at starting time between women for whom the pregnancy was their first and only (FOP) and women with no prior live births (NPLB). The null hypothesis is that the age at starting time is the same for the NPLB and FOP populations. The null hypothesis is rejected. Women with previous pregnancy failures (the NPLB group) are likely to be older than their counterparts who have never before been pregnant (the FOP group); the NPLB group tends to try repeatedly to carry a pregnancy to term. This justifies the combining of the FOP and NPLB populations into the final study population (n = 1757).

The finding that BMI was highest for women with age at menarche in the lowest category (Table 2) lends credence to sub-hypothesis 1 (page 6) and seems to support the theory that women with a higher fat content tend to begin menstruating at an earlier age. This finding should be interpreted with caution; it is possible that changes in body composition could have occurred between puberty and the starting time. BMI for this study population was calculated from height and weight *at the starting time*. However, excess weight in adolescence does often persist into young adulthood (Wada and Ueda, 1990; Srinivasan et al., 1996) and suggests that a reverse association may exist, namely that adult BMI can be used as a proxy for BMI in adolescence.

Table 2 also indicates that BMI was statistically larger in women who were older at starting time, supporting sub-hypothesis 2 (page 6), using age at starting time as a proxy measure for age at first conception. Others have found that fat content increases with age (Sarlio-Lahteenkorva and Lahelma, 1999). The finding that BMI was lowest in the highest category of completed education

(Table 2) supports sub-hypothesis 3 (page 6) and is bolstered by the findings of Sarlio-Lahteenkorva and Lahelma (1999). In their study of body mass index and social disadvantage in a representative sample of Finnish men and women aged 25-64, the authors found that the percentage of women with only a basic education (≤ 9 years) increased with increasing body mass index. They concluded that obese *women* in particular tend to face multiple social and economic disadvantages. Level of completed education was chosen in this current analysis as a proxy for socio-economic status.

Women with professional training had a significantly shorter TTP than women with other levels of completed education, suggesting an association between social advantage and fecundity. Rachootin and Olsen (1982), in a study of the socioeconomic correlates of subfecundity, also found that women without a college education were more likely to exhibit primary subfecundity than college-educated women ($p < 0.05$).

The differences in body mass index by nationality (Table 2) are likely explained by social and cultural differences. Regional differences in TTP detected in previous analysis of this data were not explainable in terms of regional differences in BMI (Juul et al. 1999).

TTP was shortest for women in the oldest category of age at starting time (Table 2) and could lead one to believe that old age at starting time increases fecundity (Table 7). However, this is likely to be a spurious association: older women who do not conceive right away may be more likely to stop trying sooner and thus would not be included in a pregnancy-based sample such as this. This

type of selection-out will result in only highly fecund older women being included in a pregnancy-based sample.

The finding that median TTP was significantly longer for women with a history of PID, gonorrhea, ovarian cysts, endometriosis, and other gynecological operations (Table 4) was expected and agrees with the published literature (Cates et al., 1994). Table 5 also indicates that women in the low (<18 kg/m^2) and high (≥ 30 kg/m^2) BMI groups and women with any previous gynecological operation (past curettage or other operations of the uterus, tubes, or ovaries) all have a significantly longer time to pregnancy ($p=0.0339$, $p=0.0476$, and $p<0.0001$, respectively). PID is a broad category of conditions and has an imprecise diagnosis (Holmes, 1998). Therefore it is likely that there is substantial overlap in these categories. A subfecund woman with a history of PID is more likely to have a history of infection (either gonorrhea or chlamydia), is more prone to endometriosis, and may seek medical attention in the form of curettage or another gynecological operation. Sexually transmitted diseases are capable of causing permanent damage to the reproductive tract (Westrom, 1994; Cates et al., 1994); endometriosis and/or therapeutic gynecological operations could confound an association between STDs and increased TTP.

The analyses support the consistent finding of an association between clinical history variables (e.g. STDs, endometriosis, and the like), and decreased fertility and fecundity.

BMI and TTP

The central hypothesis of these analyses surrounds BMI as the main predictor variable, namely that women with a higher BMI before their first and only pregnancy have a decreased waiting time to pregnancy (page 6). The finding that the median TTP was longer for the tails of the BMI distribution ($p = .0635$, Table 3, page 18) and that both BMI < 18 kg/m^2 and BMI ≥ 30 kg/m^2 significantly reduced TTP (Table 5, page 22) suggests that fecundity is highest within an ideal range of body composition (18 kg/m$^2 <$ BMI < 30 kg/m^2), lending at least partial support to the central hypothesis. Since body mass index is calculated from self-report of height and weight at the starting time, there is a potential for differential recall bias. Overweight women may be more likely to underestimate their weight. This differential misclassification, however, would tend to dilute the observed effect of BMI on TTP.

If a body mass index at the tails of the distribution increases waiting time to pregnancy, what predicts BMI? The logistic membership models indicate that every year of later age at menarche *increases* the log odds of membership in the low BMI group by 0.2560 ($p < 0.0001$); every year of later age at starting time *decreases* the log odds of membership in the low BMI group by 0.121 ($p < 0.0001$). For every 1-cigarette increase in the number of cigarettes smoked per day, the log odds of membership in the high BMI group (≥ 30 kg/m^2) increased by 0.0527 ($p < 0.0005$), suggesting that sub-hypothesis 4 (page 6) does not apply to this population. The overall model is highly significant as are the number of cigarettes smoked per day at the starting time ($p=0.0005$).

Those covariates that were significant predictors of BMI membership (Table 6) when added to the covariates included in the initial TTP proportional hazards model (Table 5), yielded a final TTP proportional hazards model (Table 7, page 25). As the age at starting time increased, there was a decrease in the degree to which fecundity was lowered; the FR increases with increasing age, however it does not exceed one until the age at starting time is greater than 40 years of age. Again, the effect in the oldest age at starting time group is likely due to selection-out (page 33). Membership in both the low and high BMI groups serves to lower fecundity and women who had onset of menses before age 10 had increased fecundity. As the number of cigarettes smoked per day increased, the more fecundity was decreased, with the exception of the highest exposure group. Significance is reached for 11 or more cigarettes per day. While Table 7 suggests that the effect of smoking at starting time on TTP is diminished in the highest level of exposure (>20 cigarettes), this is likely due to misclassification of exposure due to self-report of exposure status. Individuals who truly belong in the highest category of exposure may, upon self-report, prefer to consider themselves in the next lowest category. This would serve to artificially inflate the effect of the penultimate exposure classification and deflate any effect of the highest classification. These results suggest that not only are age at starting time, age at menarche, and cigarette smoking at starting time associated with BMI, but they also influence fecundity as measured by TTP.

Caffeine, alcohol, and cigarettes in relation to BMI and TTP

Bolumar et al. (1996) in a sister-study (population-based) to this one (pregnancy-based) found a similar association between female smoking at starting time and subfecundity as that found in Table 3, namely an increase in TTP for women smokers. The population-based sample, drawn from Denmark, Germany, Italy, Poland, and Spain detected the association in each individual country and in all countries together. Women at the upper level of exposure (≥11 cigarettes per day) were more likely to have had a TTP of more than 9.5 months (OR = 1.7, 95% CI 1.3-2.1) (Bolumar et al., 1996). Indeed, most studies have found decreased fertilization potential associated with cigarette smoking (Stillman et al.,1986; Olsen et al., 1983).

In preliminary analysis of the data, a linear model was constructed to model BMI as a continuous variable (data not shown). While the model indicated that BMI is not linear, an interrelation was noted between caffeinated coffee, the number of cigarettes smoked per day, and alcohol consumption. Cigar and pipe smoking was not included because only 1 woman was a cigar smoker and none of the women smoked pipes. In Spearman rank correlation, caffeinated coffee was significantly correlated with cigarettes ($r=.28$, $p<.0001$) and with alcohol ($r=.21$, $p<.0001$), and alcohol was significantly correlated with cigarettes ($r=.09$, $p=.0002$) (Figure 4).

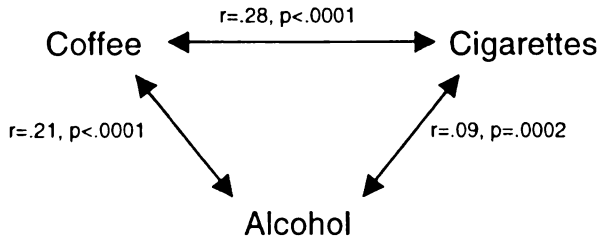


Figure 4: Spearman rank correlations between coffee, cigarette smoking, and alcohol.

To assess if one of the variables was responsible for the interrelation, partial Spearman correlations were obtained. Spearman correlations are based on ranks and are calculated for data that is not normally distributed (Rosner 1995). If an association between two of the variables disappeared while controlling for the third, the controlled variable explains the association. The relationships remained unchanged except when caffeinated coffee consumption was controlled. Partialing out caffeinated coffee caused the association between cigarettes and alcohol to disappear (r=.04, p=0.11). BMI was not correlated with either alcohol, caffeine, or cigarettes; controlling for BMI did not change the effect of coffee on the relationship between alcohol and cigarettes.

By creating a frequency matrix of the categorical variables BMI, coffee, alcohol, and cigarettes, it was noted that 53.3% of the women did not smoke at the starting time, 23.9% of the women neither smoked nor drank caffeinated coffee, and 14.6% of the women drank neither coffee or alcohol nor smoked cigarettes. To verify the role of caffeinated coffee in the interrelation, partial correlations were obtained separately when coffee consumption was zero, when

alcohol consumption was zero, and when cigarette smoking was zero; the relationship remained.

The questionnaire also obtained information on the consumption of other caffeinated beverages, namely teas and colas. To determine if the relationship existed for only caffeinated coffee or for caffeine in general, all caffeinated beverages were added together and the correlations re-assessed. The interrelations remained. When controlling for caffeinated beverages, the relationship between cigarettes and alcohol disappeared ($r=0.042$, $p=.11$). Based on the partial Spearman correlations, the interrelation between alcohol consumption and cigarette smoking seems to be mainly explained by caffeine as a third variable.

To further explore the relationship between caffeine, alcohol, and cigarettes, four separate proportional hazards regression models were created with different constructs of 2-variable interaction terms. Alcohol, caffeine, and cigarettes were each categorized into three levels of use: none (0) , moderate, and considerable. Moderate alcohol consumption was defined as 1-3 beverages per week; considerable consumption was 4 or more beverages per week. Moderate caffeine consumption was defined as 1-4 servings of caffeinated coffee, tea, or cola per day; considerable consumption was defined as 5 or more servings per day. Moderate cigarette use was defined as 1-10 cigarettes per day; considerable use was 11 or more cigarettes per day.

Four sets of two-variable interaction terms (e.g. caffeine-alcohol interaction, caffeine-cigarette interaction) were created: 2 two-level interactions, 1

three-level interaction, and one 4-level interaction (Table 10). Separate proportional hazards regression models were constructed, with time to pregnancy as the event for each set of caffeine-cigarette-alcohol interaction and including the covariates in the starting TTP model (Figure 2, step 4) (all primary predictor and clinical history variables). The zero-value terms served as the referent group. In none of the four models were any of the interaction terms close to statistical significance ($p >> 0.11$, data not shown). This suggests that interaction does not explain the relationship between caffeine, cigarettes, or alcohol; the relationship seems to be explained by caffeine consumption as a moderator variable. If caffeine consumption is not controlled in an analysis of the effects of cigarette smoking and alcohol consumption on time to pregnancy, a spurious association could appear between alcohol consumption and cigarette smoking. It might be that consumption of greater quantities of alcoholic beverages by an individual may serve to "train" the liver into metabolizing caffeine more efficiently.

Table 10--Coding for caffeine-alcohol-cigarette interaction terms

a. 2-level interactions

		Exposure 2		
		none	moderate	considerable
	none	0	0	0
Exposure 1	moderate	0	0	0
	considerable	0	0	1

b. 2-level interactions

		Exposure 2		
		none	moderate	considerable
	none	0	0	0
Exposure 1	moderate	0	1	1
	considerable	0	1	1

c. 3-level interactions

		Exposure 2		
		none	moderate	considerable
	none	0	0	0
Exposure 1	moderate	0	1	1
	considerable	0	1	2

d. 4-level interactions

		Exposure 2		
		none	moderate	considerable
	none	0	0	0
Exposure 1	moderate	0	1	2
	considerable	0	2	4

Path analysis

Path Analysis is a relatively recent addition to the set of statistical tools in the clinical sciences. The fact that the CALIS procedure in SAS can model intervening effects makes it appealing to researchers. Age at menarche (in addition to age at starting time) was retained in the final logistic model predicting membership in the low (<18 kg/m^2) BMI group (Table 6a) and may indicate that the effect of age at menarche on time to pregnancy is mediated by body mass index.

This data on TTP proposes an interesting methodologic issue: BMI appears to have an effect on TTP at the extremes of the BMI distribution. To investigate this U-shaped effect of BMI on TTP, path analysis was completed separately for two groups of the study population, namely the same two groups used in the logistic regression modeling (low vs. mid; high vs. mid). Figure 2 indicates that both age at menarche and age at starting time are statistically significant predictors of body mass index. Women with delayed menarche do have increased cycle variability ($r = 0.063$, $p = 0.018$), but there is no direct correlation between BMI (continuous or grouped) and cycle length variability ($r = 0.028$, $p = 0.29$).

The presence of an intervening effect was tested by removing BMI as both and endogenous and exogenous variable from the path analysis. An intervening effect is assumed if the parameter estimates are reduced when BMI is removed. Removal of BMI from the Low versus Mid model did not produce changes in the parameter estimates; there is little intervening effect of BMI in this model.

Removal of BMI from the High versus Mid model did produce changes in the parameter estimates. These changes suggest that BMI has an intervening effect on: age at starting time and LOGTTP (β = -.0257 reduced to β = -.0168 upon removal of BMI); on completed level of education and LOGTTP (β = .0678 reduced to β = .057 upon removal of BMI); and on alcohol consumption and LOGTTP (β = .016 reduced to β = .0139 upon removal of BMI). The parameter estimate of age at menarche *increased* upon removal of BMI (β = .0819 increased to β = .1094), suggesting that BMI is a moderator of the effect of age at menarche on LOGTTP.

As a type of linear regression, the CALIS procedure in SAS assumes that the endogenous (dependent) variable or its log and any intervening variables are normally distributed (a bell-shaped curve), and that the data fit a linear model. To test these assumptions, a linear model of TTP using the covariates in the final proportional hazards model was created (data not shown). Those covariates that were significant predictors of TTP in the survival analysis model (age at starting time < 20, age at menarche < 10, gynecological operations, and greater than 10 cigarettes per day at the starting time) were also the only variables that reached significance in the linear model; the linear model assumption is fulfilled.

The univariate tests for normality (Shapiro-Wilk, Kolmogorov-Smirnov) were all significant (H_0: the distribution is normal). However, these tests are very sensitive and the histogram of the residuals of logTTP and the normal probability plot both suggest that the distribution of logTTP is approximately normal (data not shown). The plot of residual vs. predicted plots suggests homoskedasticity.

Because body mass index is not linear, but rather U-shaped, two logistic models were used to model BMI. Within each of the logistic models, there is a linear trend between BMI and TTP. The multivariate normal distribution assumption is not fulfilled for BMI or its log. Inability to fulfill the assumption of normality for BMI may produce poor estimates in PROC CALIS (SAS, 1999).

Testing the stability of the path analysis models indicates that in each instance that age at menarche is added to the model, β-coefficients change by more than 20% in each model (Table 8, bolded coefficients), suggesting that the models may be unstable. The fact that multi-case deletion does not alter the models in the high vs. middle BMI groups is likely due to the fact that, of the five individuals that were temporarily dropped, 2 were in the low BMI group and 3 were in the middle two groups (the reference category). The two cases that had the longest value of TTP for the five deleted cases also had the lowest BMI (<18 kg/m^2), the earliest age at starting time (21 and 17 years), the lowest level of education (both left school before age 16), and smoked 10 and 20 cigarettes per day at the starting time, respectively (Table 11). For the High vs. Mid BMI group, age at menarche still has its effect on the β-coefficients in the models, but the effect is not due to outliers (Tables 9c and 9d versus Tables 8c and 8d). The difference noted for the Low vs. Mid BMI group (Tables 9a and 9b versus Tables 8a and 8b) suggests that the effect of age at menarche on the stability of the model is due, at least in part, to the presence of outliers.

Table 11: Characteristics of deleted cases

Case	Age at Menarche (yrs)	Age at Starting Time (yrs)	BMI (kg/m^2)	Smoking at Starting Time (Cigarettes/day)	Completed Level of Education	TTP (months)
1	19	21	17.10	10	left before age 16	94.0
2	19	17	17.69	20	left before age 17	8.0
3	21	29	20.57	0	university degree	2.1
4	22	22	21.72	3	professional training	2.0
5	23	24	24.84	0	professional training	0.5

Chapter 5

METHODOLOGIC CONSIDERATIONS

Does age at interview confound the effect of age at starting time?

In general, the earlier a woman begins trying to achieve pregnancy the earlier she tends to succeed (Table 2). In this regard, current age (age at interview) could potentially confound a relationship between age at starting time and BMI if it is correlated both with body mass index and time to pregnancy. The age at which BMI was obtained is unavailable. The questionnaire merely asks "What was your height and weight before this pregnancy" (Appendix A). The Spearman rank correlation for age at interview and BMI was $r = 0.065$, $p=.0071$, based on 1728 observations. Though the correlation is small, it is statistically significant. Typically, this confounding could be determined in linear regression by evaluating the change in regression parameters as age at interview is added to the model. Indeed, using linear regression to model BMI as a continuous variable, age at interview does confound the association between starting time and BMI.

However, for the purposes of this analysis two *logistic* models were constructed with BMI as the dependent variable: one that models membership in the left tail (<18 kg/m^2) versus a middle group (18-30 kg/m^2), and one that models membership in the right tail (≥ 30 kg/m^2) versus the middle group. The potential confounding effect of age at interview was assessed by re-creating these logistic models with both age at interview and age at starting time in the

starting model and then without age at interview in the final model, yet retaining the variables that previously had remained in the model after confounder assessment. As before, the difference in the likelihood ratios follows a Chi-square distribution with df = $df_{\text{starting model}}$ - $df_{\text{reduced model}}$. For both of these models, removal of age at interview does not yield a significant p-value for the Chi-square test; in both instances $.25 < p < .50$ and suggests that age at interview can be removed from the model.

Age at interview and age at starting time are more closely correlated in the middle of the BMI distribution but begin to diverge at the tails of the BMI distribution (and the TTP distribution). The results of the analyses carried out in this project have demonstrated that membership in the middle BMI groups does not seem to affect TTP. The median time to pregnancy in the left tail (<18 kg/m^2) is significantly different from the middle (Table 3); the same is not true, however, for the right tail (≥ 30 kg/m^2). Using the 18-25 kg/m^2 group as the reference, the fecundability ratio for the 25-30 kg/m^2 BMI group in the proportional hazards model is close to 1 (FR=1.028), and not statistically significant (p=0.73). Therefore, because this analysis: a.) uses logistic regression in the modeling of BMI; b.) is concerned only with the tails of the distribution of BMI (and thus the middle of the distribution serves as the reference in modeling); c.) demonstrates that age at interview falls out of both BMI models using a Chi-square test for confounders; and d.) demonstrates that only the lowest two groups of age at starting time (<20, and 21-25) are significant in the TTP proportional hazards

model, age at interview confounds neither the association between age at starting time and BMI nor the association between age at starting time and TTP.

Pregnancy-based versus population-based sampling

As a study of subfecundity, the study population consists only of pregnant or recently pregnant women and therefore, by design, does not include those women who never actually conceived. It is not expected that the "exposures" examined in this analysis lead to sterility. Indeed, this analysis would not be capable of detecting such effects. Rather, it is hypothesized that they have an impact on the period of time it takes for a couple to conceive. A pregnancy-based sample is capable of detecting such shifts in the data distribution (Bolumar et al. 1996).

A pregnancy-based survey has the advantage of reducing information bias. The pregnancy is a recent (or even on-going event) and memories surrounding conception will likely be fresh. Additionally, because all women in the study conceived, there is no differential recall for women who did conceive versus those who did not.

Chapter 6

CONCLUSIONS

This pregnancy-based, cross-sectional study suggests fecundity, as measured by time to pregnancy, is highest within an ideal range of body composition. Membership in this ideal range of BMI can be predicted for the study population by the year at which menses began, the year at which women began having intercourse without doing anything to avoid pregnancy, and the number of cigarettes smoked at the starting time. Cigarette smoking, previous gynecological operations, and early age at starting time significantly reduce fecundity as measured by time to pregnancy. Path analysis suggests that the effects of age at starting time, completed level of education, and alcohol consumption on time to pregnancy in the high BMI population (≥ 30 kg/m^2) are mediated by body mass index.

It is estimated that in the year 2000, there will be approximately 5.13 million women in the United States with impaired fecundity, defined by the National Center for Health Statistics to include women who: are unable to have a baby due to reasons other than surgical sterilization; report difficulty conceiving or delivering a baby or that they had been told a pregnancy was dangerous to them and/or the baby; and/or were continuously married and did not conceive after 36 months of intercourse without contraception (Stephen, 1996). Additionally, the prevalence of obesity in the United States (15%) is significantly higher than in European countries (7% in France and 9% in the United Kingdom)

Women are also more commonly very obese (more than 50% overweight) (Laurier et al., 1992). Only 53 of the 1757 women (3%) in this study had a BMI ≥ 30 kg/m^2, yet their time to pregnancy was significantly increased. While the population utilized in this investigation is not representative of all European women, the results do suggest that obesity may particularly important in fertility and fecundity; this role is likely amplified in a heavier population such as that found in the United States.

APPENDICES

APPENDIX A

ESIS QUESTIONNAIRE ON PREGNANCY AND FERTILITY

Questionnaire on Pregnancy and Fertility

(for women who have recently given birth)

The purpose of these questions is to learn more about how easily women who want to have children get pregnant. Also we intend to find out whether the time it takes to become pregnant is related to factors such as working conditions, life-style or medical reasons. We can thus try to identify any avoidable risks of infertility.

Most questions relate to the time leading up to your recent pregnancy. Please fill in the questionnaire as best as you can. We appreciate your help.

The information you will give is anonymous and strictly confidential. Your name is not recorded together with your answers. Many women will be interviewed and your answers will be totalled up with theirs.

Your participation is, of course, voluntary.

It will take approximately 10 to 15 minutes to complete this questionnaire.

Sign.

Note: **This questionnaire is intended for women who have recently given birth to a child.**

If you have not recently given birth, please give the questionnaire back.

Instructions for filling in the questionnaire

For some questions, please put a cross or a tick in the box next to the answer that best describes you or your experience. For example:

G7. What was your pattern of work?

daytime (with or without flexi-time) ..... ☐ 1

evening ..... ☐ 2

night ..... ☐ 3

shift-work (changing or rotating) ..... ☐ 4

Or enter dates or durations (Year/month) of events. For example:

A7. When were you born?

Month:_____ Year: 19_____ *(meaning August 1962)*

A8. How long did it take you to become pregnant?

Weeks:_____ Months:_____ Years:_____ *(meaning 3½ months)*

Sometimes your answer will allow you to skip certain questions or sections of questions. **Please read the *"GO TO –>"* statements carefully to make sure you answer all the appropriate questions.**

For example:

GO TO –> question G5 on page 7

SECTION A: Your recent pregnancy

A1. Please write today's date here:

Day:_____ Month:_____ Year:_____ A1D,A1M,A1Y

A3. When was the baby born?

Day:_____ Month:_____ Year:_____ A3D,A3M,A3Y

A4. How many weeks or months were you pregnant?

Pregnant for: weeks:_____ *and/or* Months:_____ A4W,A4M

A5. Where do you live now? (just give the town or city, not the street)

A5

The following questions consider the interval before this pregnancy

SECTION B: Pregnancy and contraception

Below are some statements about the way you became pregnant. Choose the one that best describes how you became pregnant. Then tick the box and skip to the page indicated.

This was your first pregnancy, and:	You had been pregnant before this pregnancy, and:
You have never used a birth control method (such as the pill, condoms, or rhythm method).	After your previous pregnancy, your menstrual periods started again. Since then, you have used no birth control methods (such as the pill, condoms, or rhythm method).
☐ 1 *GO TO —> Section D, page 59*	☐ 4 *GO TO —> Section F, page 61*
You became pregnant while using a birth control method (regularly or irregularly).	You became pregnant while using a birth control method (regularly or irregularly). Note: Breast-feeding is not a birth control method.
☐ 2 *GO TO —> Section C, page 58*	☐ 5 *GO TO —> Section C, page 58*
You used to use birth control, and you became pregnant since you gave it up.	After your previous pregnancy your menstrual periods started again. Since then you used birth control for a time, gave it up, and then became pregnant.
☐ 3 *GO TO —> Section D, page 59*	☐ 6 *GO TO —> Section D, page 59*
	Your periods did not start again since your previous pregnancy. You were not using birth control when you became pregnant.
	☐ 7 *GO TO —> Section E, page 60*

B1

You should have ticked one of the above boxes. If not, please try again.

SECTION C

Questions for you if you became pregnant in spite of using birth control (regularly or irregularly).

If this is not true, go back to page 57 and check your answer.

C1. What kind of birth control were you using around the time you became pregnant?
(You may mark more than one)

Rhythm method (safe periods)	☐ 1	C1A
Withdrawal (coitus interruptus)	☐ 1	C1B
Coil (intra-uterine device)	☐ 1	C1C
The Pill (oral contraceptive)	☐ 1	C1D
Condom	☐ 1	C1E
Cap (diaphragm)	☐ 1	C1F
Contracpetive injection or implant	☐ 1	C1G
Jelly, cream or foam	☐ 1	C1H
Other	☐ 1 *(Please write below)*	C1I

C2. Were you using the birth control in a regular and consistent manner when you became pregnant?

No, not quite regularly	☐ 1	C2
Yes, regularly and consistently	☐ 2	

C3. For how long were you using the birth control up to your pregnancy? (Any of the methods you ticked above)

Months:_____ *and/or* Years:_____ C3M,C3Y

C4. Now write in the box below the month and year your pregnancy started. We call this the "STARTING TIME"
STARTING TIME: C4M,C4Y

Month: _____ Year: 19_____

NOW GO TO: —> Section G on page 63

SECTION D

Questions for you if you were not using any birth control when you became pregnant.

If that is not true, go back to page 57 and check your answer.

D1. Leading up to this pregnancy, when was it that you started having sexual intercourse without using any birth control to prevent pregnancy?

We call this the "STARTING TIME"

STARTING TIME: D1M,D1Y

Month: _____ Year: 19_____

D2. How long was it from that "STARTING TIME" until you became pregnant?

(The date you became pregnant is the date you conceived).

How long?

Weeks:_____ *and/or* Months:_____ *and/or* Years:_____ D2W,D2M,D2Y

D3. To put it differently: How many periods did you have between the "STARTING TIME" and you becoming pregnant?

No periods..... ☐ 0 D3

1 period..... ☐ 1

2 periods..... ☐ 2

3 periods..... ☐ 3

More than 3 periods..... ☐ 4

NOW GO TO: —> Section G on page 63

SECTION E:

Questions for you if your periods had not started again when you became pregnant.

If this is not true, go back to page 57 and check your answer.

E1. Now write in the box below the month and year your pregnancy started.

We call this the "STARTING TIME"

STARTING TIME: E1M,E1Y

Month: _____ Year: 19____

NOW GO TO: —> Section G on page 63

SECTION F:

Questions for you if you used no birth control method since your previous pregnancy.

If this is not true, go back to page 57 and check your answer.

F1. When was it that you started having sexual intercourse after your previous pregnancy?

Month: _____ Year: 19____

F1M,F1Y

F2. At that time (when having sexual intercourse again): Had your menstrual periods restarted?

☐ 1 Yes

▼

We call the time you started having sexual intercourse again after your previous pregnancy the "STARTING TIME".

☐ 2 No

▼

Now work out approximately the month and year when your periods returned after your previous pregnancy. We call this the "STARTING TIME".

F2

STARTING TIME:

Month: _____ Year: 19____

F2M,F2Y

F3. How long was it from that "STARTING TIME", until you became pregnant?

(The date you became pregnant is the date you conceived).

How long?

Weeks:_____ *and/or* Months:_____ *and/or* Years:_____

F3W,F3M,F3Y

F4. To put it differently: How many periods did you have from the "STARTING TIME" up to you becoming pregnant?

No periods	☐ 0	F4
1 period	☐ 1	
2 periods	☐ 2	
3 periods	☐ 3	
More than 3 periods	☐ 4	

NOW GO TO: ***—> Section G, page 63***

SECTION G:

Questions about life and work at the "STARTING TIME"

G1. You have just stated what we call your "STARTING TIME". Please write again this date in the box:

STARTING TIME: G1M,G1Y

Month: _____ Year: 19____

G2. Did you have a paid job at the "STARTING TIME"?
(Do not consider jobs started only since the "STARTING TIME"). G2

No ..... ☐ 1 ***GO TO —> question G11, page 67***

Yes ..... ☐ 2

G3. In what kind of industry or business were you working?
(Please be as precise as possible)

G4. What was your job-title?
(Please be as precise as possible: Do not fill in just 'nurse', write 'psychiatric nurse')

G5. What kind of work did you do? *(Please be as precise as possible)*

G5A,G5B

G6. For how many hours per week did you work on average?

Hours per week:..... _____ G6

G7. What was your pattern of work?

Daytime
(with or without flexi-time) ..... ☐ 1 G7

Evening ..... ☐ 2

Night ..... ☐ 3

Shift-work
(changing or rotating shifts) ..... ☐ 4

G8. Did your job at the "STARTING TIME" involve any working with VDUs (computers or word processors with a screen)?

No ..... ☐ 00

Yes **How many hours per week?** _____ (average) G8

G9. How often did you come into contact with the following exposures in your job?

(You should tick one box for each exposure)

G9A-P

		never	occasionally	from time to time each day	most of your working week
a.	**Paints, varnish, lacquer**	1	2	3	4
b.	**Dyes, pigments, inks**	1	2	3	4
c.	**Solvents**	1	2	3	4
d.	**Degreasing or drycleaning agents**	1	2	3	4
e.	**Resins, adhesives**	1	2	3	4
f.	**Petrol, petrochemicals**	1	2	3	4
g.	**Cutting, lubricating oils**	1	2	3	4
h.	**Welding fumes**	1	2	3	4
i.	**Metal dusts, fumes**	1	2	3	4
j.	**Engine exhaust**	1	2	3	4
k.	**Pesticides, fungicides, insecticides, weedkillers**	1	2	3	4
l.	**Wood preserving materials**	1	2	3	4
m.	**Anesthetic gases**	1	2	3	4
n.	**Radioactivity or x-rays**	1	2	3	4
o.	**Sterilizing gases (ethylenoxide etc.)**	1	2	3	4
p.	**Loud noise**	1	2	3	4

Others *(please specify):*

Briefly describe how you came in contact with these substances, giving if possible their names:

[Item k may be split in three. Explanation attached]

G10. The following questions are about how you experienced your job situation at the "STARTING TIME". Please answer each question by ticking the one box that best fitted your job situation.
Sometimes none of the answers fits exactly. Please choose the answer that comes closest.

G10A-N

		Strongly disagree	Disagree	Agree	Strongly agree
a.	My job required that I learnt new things	1	2	3	4
b.	My job involved a lot of repetitive work	1	2	3	4
c.	My job required me to be creative	1	2	3	4
d.	My job required a high level of skill	1	2	3	4
e.	On my job, I had very little freedom to decide how I did my work	1	2	3	4
f.	I had a lot of say about what happened on my job	1	2	3	4
g.	My job required lots of physical effort	1	2	3	4
h.	I was not asked to do an excessive amount of work	1	2	3	4
i.	I had enough time to get the job done	1	2	3	4
j.	I was often required to move or lift heavy loads on my job	1	2	3	4
k.	My job was very hectic	1	2	3	4
l.	I was often required to work for long periods with my body in physically awkward positions	1	2	3	4
m.	On my job I was often told that I was doing a good job	1	2	3	4
n.	On my job I was often treated unfairly by another person	1	2	3	4

G11. At the "STARTING TIME": Did you smoke?

☐ 1 Yes

↓

What?	How many per day?
Cigarettes:	_____ per day
Cigars:	_____ per day
Pipe tobacco:	_____ per day

☐ 2 No G11

G11A-C

↓

Did you smoke before then?

☐ 1 No ☐ 2 Yes G11D

When did you quit smoking?

Month:_____ Year: 19_____

G11M,G11Y

G12. At the "STARTING TIME": Were you exposed to other people's cigarette smoke?

At work? ..... ☐ 1 Yes ☐ 2 No G12A

Outside work? ..... ☐ 1 Yes ☐ 2 No G12B

G13. For each of the following drinks, how much did you drink at the "STARTING TIME"?

Caffeinated coffee:..... _____ cups per DAY G13A

Decaffeinated coffee..... _____ cups per DAY G13B

Tea: ..... _____ cups per DAY G13C

Cola: ..... _____ glasses/cans per DAY G13D

Beer: ..... _____ glasses/bottles per WEEK G13E

Wine:..... _____ glasses per WEEK G13F

Spirits:..... _____ glasses per WEEK G13G

Aperitifs/sherry/port:..... _____ glasses per WEEK G13H

G14. Where did you live at the "STARTING TIME"? (just town or city, not street)

G14

G15. Since when have you lived in this area?

Month:_____ Year: 19_____ [G15M,G15Y]

SECTION H: Questions about the father of your child.

The following questions refer to his life and work at your "STARTING TIME".

H1. At the "STARTING TIME": Did your child's father smoke?

☐ 1 Yes ↓ ☐ 2 No H1

☐ 9 Don't know

What?	How many per day?	
Cigarettes:	_____ per day	H1A
Cigars:	_____ per day	H1B
Pipe tobacco:	_____ per day	H1C

H2. For each of the following drinks, around the "STARTING TIME", how much did he drink?

Beer:..... _____ glasses/bottles per WEEK H2A

Wine..... _____ glasses per WEEK H2B

Spirits:..... _____ glasses per WEEK H2C

Aperitifs/sherry/port:..... _____ glasses per WEEK H2D

Don't know ..... ☐ 99

H3. Was he practising any sport or hobby for which he exercised physically?

☐ 00 No ☐ Yes

For how many hours per week on the average?

_____ hours per week [H3]

H4. When was he born?

Year: 19_____ H4

Don't know ..... ☐ 99

H5. In which town and country was he born?

Don't know ..... ☐9 H5

H6. Is he presently under education?

☐0 No ☐ Yes H6

Which education?

Still in school ..... ☐1

Post school training in a manual trade (eg apprenticeship) ..... ☐2 *Write education below*

Post school training in a profession (eg nursing) ..... ☐3 *Write education below*

University education ..... ☐4 *Write education below*

Other education ..... ☐5 *Write education below*

H7. What is the last education or training he has completed?

Left school at age 15 or before, no further education ..... ☐1 H7

Left school at 16 or 17, no further education ..... ☐2

Left school at 18 or older, no further education ..... ☐3

Post school training in a manual trade (eg apprenticeship) ..... ☐4 *Write education below*

Post school training in a profession (eg nursing) ..... ☐5 *Write education below*

University degree ..... ☐6 *Write education below*

Other ..... ☐7 *Write education below*

Don't know ..... ☐9

H8. Did he have a paid job at your "STARTING TIME"?

Yes ..... ☐ 1 H8

No ..... ☐ 2 —> ***GO TO section K, page 74***

Don't know ..... ☐ 9 —> ***GO TO section K, page 74***

H9. In what kind of industry or business did he work?

(Please be as precise as possible)

H10. What was his job-title?

(Please be as precise as possible: Do not just fill in 'welder', write 'steel-welder')

H11. What kind of work did he do? *(Please be as precise as possible)*

H11A,H11B

H12. For how many hours per week did he work on average?

Hours per week: _____ H12

H13. What was his pattern of work?

Daytime
(with or without flexi-time) ..... ☐ 1 H13

Evening ..... ☐ 2

Night ..... ☐ 3

Shift work
(changing or rotating) ..... ☐ 4

H14. At the "STARTING TIME", did your partner drive a vehicle regularly?

☐ 0 No ☐ Yes H14

What kind of vehicle?

Car or taxi ..... ☐ 1

Bus ..... ☐ 2

Van ..... ☐ 3

Lorry ..... ☐ 4

Other ..... ☐ 5 *Please specify:*

For how many hours a day did he drive on the average?

Hours per day: ..... _____ H14A

H15. Was his work at the "STARTING TIME" mostly seated or standing?

Mostly seated in a chair ..... ☐ 1 H15

Mostly standing ..... ☐ 2

Both seated and standing ..... ☐ 3

Mostly seated in a vehicle ..... ☐ 4

Other ..... ☐ 5 *Please specify:*

H16. Which of the following exposures did he come into contact with in his job?

(You should tick one box for each exposure) H16A-Q

		No	Yes	Don't know
a.	**Paints, varnish, lacquer**	1	2	3
b.	**Dyes, pigments, inks**	1	2	3
c.	**Solvents**	1	2	3
d.	**Degreasing or drycleaning agents**	1	2	3
e.	**Resins, adhesives**	1	2	3
f.	**Petrol, petrochemicals**	1	2	3
g.	**Cutting, lubricating oils**	1	2	3
h.	**Welding fumes**	1	2	3
i.	**Metal dusts, fumes**	1	2	3
j.	**Engine exhaust**	1	2	3
k.	**Pesticides, fungicides, insecticides, weedkillers**	1	2	3
l.	**Wood preserving materials**	1	2	3
m.	**Anesthetic gases**	1	2	3
n.	**Radioactivity, x-rays**	1	2	3
o.	**Sterilizing gases (ethylenoxide etc.)**	1	2	3
p.	**Loud noise**	1	2	3
q.	**Heat**	1	2	3
	Others *(please specify below)*	1	2	3

Briefly describe – if you can – how he came in contact with these substances, giving if possible their names:

[Item k may be split in three. Explanation attached]

SECTION K: Health factors

K1. Around your "STARTING TIME": How long was it from the start of one menstrual bleeding to the start of the next bleeding?

Number of days:_____ *or* K1A,K1B

Between _____ and _____ days

No bleeding at all ☐ 0000

I can't remember, don't know ☐ 9999

K2. At your "STARTING TIME", how often did you have sexual intercourse?

Daily ☐ 1 K2

At least once a week ☐ 2

Two to four times a month ☐ 3

Less than twice a month ☐ 4

I can't remember ☐ 5

I don't want to answer ☐ 6

K3. Did you plan to have a baby at that time?

☐ 1 Yes ☐ 2 Undecided ☐ 3 No K3

K4. Did you or your partner seek any medical or professional advice to help you to become pregnant?

☐ 1 Yes ☐ 2 No K4

K5. How long had you been attempting to become pregnant when you sought this advice?

Months:_____ *and/or* Years:_____ K5M,K5Y

K6. Have you given birth to any children before this pregnancy?

No ..... ☐ 00 K6

Yes ..... **How many?** _____ (number of liveborn children)

K7. Did you ever have a cesarean section before this pregnancy?

No ..... ☐ 0 K7

Yes ..... **How many?** _____ (number of cesarean sections)

K8. Have you ever had any miscarriages? (Don't include miscarriages you are uncertain about)

No ..... ☐ 00 K8

Yes ..... **How many** _____ (number of miscarriages)

K9. Have you ever had any pregnancies outside the uterus (ectopic pregnancies)?

No ..... ☐ 0 K9

Yes ..... **How many** _____ (number of ectopic pregnancies)

K10. Have you ever had any stillbirths?

No ..... ☐ 0 K10

Yes ..... **How many?** _____ (number of stillbirths)

K11. Did any of your children die within the first 7 days after birth?

No ..... ☐ 0 K11

Yes ..... ☐ 1

K12. Have you ever had any induced abortions (terminations)?

No ..... ☐ 00 K12

Yes ..... **How many?** _____ (number of induced abortions)

K13. All in all: How many times have you been pregnant (including your last pregnancy)?

I have been pregnant..... _____ times K13

K14. How old were you, when you had your first menstrual periods?

Age: ..... _____ years old K14

I never had menstrual periods..... ☐ 00

I can't remember, I don't know..... ☐ 99

K15. Have you ever been told by a doctor that you have had any of the following infections, diseases or operations?

Tick the NO or YES box for each one. If YES, please give the year for the first time.

		No	Yes	Year first time	
a.	**PID: Pelvic inflammatory disease (eg. infection in fallopian tubes or ovaries)**	☐ 1	☐ 2	19_____	K15A K15AY
b.	**Chlamydia infection**	☐ 1	☐ 2	19_____	K15B K15BY
c.	**Gonorrhea infection**	☐ 1	☐ 2	19_____	etc.
d.	**Other sexually transmitted diseases**	☐ 1	☐ 2	19_____	
e.	**Ovarian cysts**	☐ 1	☐ 2	19_____	
f.	**Fibroids, myomas**	☐ 1	☐ 2	19_____	
g.	**Endometriosis**	☐ 1	☐ 2	19_____	
h.	**Thyroid disease**	☐ 1	☐ 2	19_____	
i.	**Diabetes**	☐ 1	☐ 2	19_____	
j.	**Removal of appendix (appendectomy)**	☐ 1	☐ 2	19_____	
k.	**Pelvic infections after former pregnancies**	☐ 1	☐ 2	19_____	
l.	**Chemical or radiation therapy because of cancer**	☐ 1	☐ 2	19_____	
m.	**Curettage**	☐ 1	☐ 2	19_____	
n.	**Other operations of the uterus, tubes or ovaries**	☐ 1	☐ 2	19_____	K15N K15NY

K16. Have you ever used the IUD coil for birth control?

☐ 0 No, never ☐ Yes K16

How many times inserted? _____

How long in total?

Months:_____ *and/or* Years:_____ K16M,K16Y

K17. Have you ever used the pill for birth control?

☐ 0 No, never ☐ 1 Yes K17

When did you stop using the pill for the last time?
(please be as precise as possible)

Month:_____ Year: 19_____ K17M,K17Y

K18. What was your height and weight before this pregnancy?

Height: ..... _____ cm K18A

Weight: ..... _____ kg K18B

SECTION L: General questions

L1. What is your year of birth?

Year: 19_____ L1

L2. Are you married?

No, unmarried ..... ☐ 1 L2

Yes, married ..... ☐ 2

L3. In which town or country were you born?

L3

L4. Do you belong to any religion?

☐ 0 No

☐ Yes [L4]

↓

Which religion? _____

L5. Regarding your attitude towards marriage, partnership and sexuality: Do you follow your religion's recommendations?

No ..... ☐ 1 [L5]

Yes ..... ☐ 2

Don't know ..... ☐ 3

L6. Are you presently under education?

☐ 0 No

☐ Yes L6

Which education?

Still in school ☐ 1

Post school training in a manual trade (eg apprenticeship) ☐ 2 *Write education below*

Post school training in a profession (eg nursing) ☐ 3 *Write education below*

University education ☐ 4 *Write education below*

Other education ☐ 5 *Write education below*

L7. What is the last education or training you have completed?

Left school at age 15 or before, no further education ☐ 1 L7

Left school at 16 or 17, no further education ☐ 2

Left school at 18 or older, no further education ☐ 3

Post school training in a manual trade (eg apprenticeship) ☐ 4 *Write education below*

Post school training in a profession (eg nursing) ☐ 5 *Write education below*

University degree ☐ 6 *Write education below*

Other ☐ 7 *Write education below*

END: Thank you very much for the information and for your patience

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