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Pubertal timing – antecedent to risk or resilience?

Epidemiological studies on growth, maturation and health risk behaviours; The Young HUNT study, Nord-Trøndelag, Norway

Thesis for the degree of philosophiae doctor

Trondheim, July 2007

Norwegian University of
Science and Technology
Faculty of Medicine
Department of Public Health and General Practice, HUNT
Research Centre

NTNU
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HiNT
NORD-TRØNDELAG UNIVERSITY COLLEGE

NTNU
Norwegian University of Science and Technology

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ISBN 978-82-471-3487-0 (printed ver.)
ISBN 978-82-471-3490-0 (electronic ver.)
ISSN 1503-8181

Theses at NTNU, 2007:159

Printed by Tapir Uttrykk

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Contents

Acknowledgements

I want to thank all boys and girls who participated in the Young HUNT 1(1995-1997) and Young HUNT 2 study (2000-2001), whom actually made this research work and thesis feasible. The adolescent part of the Nord-Trøndelag Health Study (Young HUNT) is a collaboration between HUNT Research Centre, Faculty of Medicine, The Norwegian University of Science and Technology (NTNU), The Norwegian Institute of Public Health, and Nord-Trøndelag County Council. Financial support has been granted by the Norwegian Research Council, the Nord-Trøndelag University College (HINT) and the Department of Public Health and General Practice, NTNU.

After finishing my post-graduate thesis at NTNU in June 2001 as Master of Arts (MA), I started as a lecturer at HINT, at the division for nurse studies. During fall 2002, my supervisor during the MA work, Professor Lars Vatten, NTNU, offered me the opportunity to further scientific graduation as research fellow at the Department of Public Health and General Practice, Faculty of Medicine, NTNU. He has been my main supervisor and I am grateful to him for sharing his knowledge in epidemiology and scientific research with me. That includes his theoretical and practical guidance, but also his skills in scientific writing and how to improve readability, which has been very valuable for me as research fellow. My gratitude also goes to his research colleague at the Department of Public Health and General Practice, co-author Tom Ivar Lund Nilsen, who has provided vital help with statistics and proper interpretations, but also critically reviewed drafts and manuscripts.

I am also grateful for the support that I have received from all my colleagues at the HUNT Research Centre. Especially, I would like to thank Associate Professor Turid Lingaas Holmen, who has been my collaborating partner and co-author of all scientific papers included in this thesis. As project manager for Young HUNT, specialist in paediatrics, along with her scientific skills and personal engagement, she has been an invaluable resource during this work. I also want to thank Bitte Dillan, Inger D.Holbø and Aina Enes for practical assistance, but also for their friendliness. The Head Manager

at the HUNT Research Centre, Professor Jostein Holmen, has been another source of knowledge and inspiration. According to him, nothing is ever impossible, and I am thankful for that.

Finally, I want to thank my family Gunnar, Kristoffer, Magnus, and Erika for their support and love. A special thank goes to Erika for being the most patient daughter. Being a teenager herself, she has for years had to deal with a mother preoccupied with puberty and pubertal changes. I do feel privileged!

Abbreviations and definitions

AAM	Age at menarche
APHV	Age at peak height velocity
BMI	Body Mass Index
CI	Confidence interval
EPIC	European Prospective Investigation into Cancer and Nutrition
DEXA	Dual Energy X-ray Apsorptiometry
GH	Growth Hormone
HUNT	The Nord-Trøndelag Health Study
IGF	Insulin Growth Factors
IOTF	International Obesity Task Force
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PDS	Pubertal Developmental Scale
PROS	Pediatric Research in Office Settings
SD	Standard deviation
SES	Socio Economic Status
SIRUS	Norwegian Institute for Alcohol and Drug Research
SM timing	Timing of sexual maturation
Young HUNT	The adolescent part of HUNT
WHO	World Health Organisation

Risk and resilience:

Risk factors are those conditions or variables associated with a higher likelihood of negative and undesirable outcomes, i.e. variables that can comprise health, wellbeing or social performance while resilience is a person's ability to withstand risk[12].

List of papers

I. Bratberg GH, Nilsen TI, Holmen TL, Vatten LJ. Sexual maturation in early adolescence and alcohol drinking and cigarette smoking in late adolescence: a prospective study of 2,129 Norwegian girls and boys. *Eur.J Pediatr* 2005;164:621-5.

II. Bratberg GH, Nilsen TIL, Holmen TL, Vatten LJ. Perceived pubertal timing, pubertal status and the prevalence of alcohol drinking and cigarette smoking in early and late adolescence: a population based study of 8950 Norwegian boys and girls. *Acta Paed* 2007;96(2):292-5.

III. Bratberg GH, Nilsen TIL, Holmen TL, Vatten LJ. Early sexual maturation, central adiposity and subsequent overweight in late adolescence. A four-year follow-up of 1605 adolescent Norwegian boys and girls: the Young HUNT study. *BMC Public Health* 2007,7:54

IV. Bratberg GH, Nilsen TI, Holmen TL, Vatten LJ. Combined influence of early sexual maturation and central adiposity on subsequent stature : A four-year follow-up of 1,605 Norwegian boys and girls: the Young-HUNT study. *Eur.J Pediatr* 2006;165:787-93

Summary

Background: The timing of pubertal milestones influences the tempo and progression of growth and maturation, which in turn have consequences for boys' and girls' body size, shape and composition. Early sexual maturation has been associated with overweight and a shorter adult stature. The biological mechanisms underlying these associations are not clear, but since adipose children tend to mature earlier than leaner children, subsequent changes in height and weight could be attributed to nutrition in childhood rather than to early sexual maturation.

The rapid bodily changes and the timing of these changes may also have an impact on boys' and girls' self-concepts, their social functioning, roles and behaviours. Early maturation is considered a risk factor for early initiation and advancement in use of alcohol and tobacco in adolescence, but is not clear if these differences persist over time. It has also been unclear whether adolescents' perceptions of their own pubertal timing play an important role for how they actually act. Most studies concerned with pubertal timing as antecedent to risk or resilience, have been conducted on girls.

The main aims of this thesis are:

- To estimate the prevalence of advanced (risky) alcohol drinking and cigarette smoking in late adolescence related to the timing of sexual maturation and gender (Paper I and II).
- To investigate whether the timing of sexual maturation in both genders, independently or in concert with early central adiposity, affects final height (Paper IV) or the prevalence of overweight (Paper III) as assessed in late adolescence.

Material and method: To address these questions we used data from the Young HUNT 1 study (1995-1997) (Paper I,II,III,IV), and the Young HUNT 2 study carried out about four years later (Paper I, III, IV), in addition to data from the Medical Birth Registry of Norway and the adult part of the HUNT 2 study

(Paper IV). A total of 9097 students (92%) from all middle and high schools in Nord-Trøndelag county participated in the Young HUNT 1 study and 8950 students completed the questionnaire. Among those, 2399 boys and girls were followed from early (baseline) to late adolescence (follow-up). Both the baseline and follow-up study included questionnaire data and physical examinations of height, weight, and waist and hip circumference. Age at menarche (AAM), the Pubertal Developmental Scale (PDS) and perceived pubertal timing were used to classify the timing of sexual maturation (SM timing). Baseline waist circumference was used to classify central adiposity (Paper III and IV), and body mass index (BMI) was used to classify overweight. Descriptive statistics as well as multivariate logistic regression modelling (Paper I, II and III) and general linear modelling (Paper III and IV) were applied to study the associations between exposures and outcomes.

Results: Girls, who had matured early (OR 1.7, CI 1.2-2.4) or late (OR, 1.5, CI 1.1-2.2) were both more likely to report advanced drinking in late adolescence, compared to on time matured counterparts. Late matured boys were less likely (OR 0.5, CI 0.3-0.8) to engage in advanced drinking. Daily smoking was also more common among girls who had matured early (OR 1.5, CI 1.1-2.2), than among girls who were on time (Paper I). Boys and girls who perceived themselves as early matured were more likely to report risky drinking than those who perceived themselves as being on time, both in middle school and high school. A nearly identical pattern was found for smoking (Paper II).

Early sexual maturation in girls, but not in boys, was associated with overweight. This association, however, was restricted to girls with high waist circumference (>median) at baseline (OR, 2.7, CI 1.5-4.9). Early matured boys and girls with high waist were on average 5.7 cm and 3.6 cm taller than early maturing boys and girls with low waist circumference. Height was lowest in early matured boys (176.6 cm) and girls (163.8 cm) with a lean body composition at baseline. Height gain during follow-up was closely related to SM timing, but independent of central adiposity. Differences in height and weight related to central adiposity were more pronounced among those who matured early, compared to those who were intermediate or late matured (Paper III and IV).

Conclusions:

- Early (or rapid) maturation in girls constitutes a risk factor for advanced alcohol drinking and cigarette smoking not only in early adolescence, but also in late adolescence.
- Perceptions of being earlier matured than same aged peers may increase the risk of alcohol drinking and cigarette smoking, especially in combination with high pubertal status.
- The combination of early age at menarche and central adiposity increases girls' likelihood of being overweight in late adolescence.
- The combination of early sexual maturation and leanness yields short adult stature.

1.0 Introduction

During the end of the twentieth century, there was a change in our view of adolescence from a time of inherent stress and storm to one of opportunities for growth and positive development. At the same time, many adolescents around the world are threatened by poverty, violence, alienation and limited opportunities for the future. Several features of the adolescent decade may make this period challenging, and also the extent and timing of biological, psychological and social changes may be overwhelming and stressful to some adolescents[1]. Early sexual maturation, especially in girls in Western societies, has been associated with a variety of negative health and psycho-social outcomes[2;3].

From a public health point of view the common use of alcohol and tobacco among adolescents is of great concern. These behaviors may, due to their high prevalence and positive association with social and domestic problems, influence boys' and girls' life course and ability to achieve good health[4]. Another current feature is the extent and severity of the global overweight epidemic, which has refocused interest on the natural history of disease and put emphasis on adolescence as a particularly critical period for the development and persistence of obesity[5;6].

In this thesis, concepts and methods from epidemiology are applied to explore the relation between the timing of sexual maturation (SM timing) and health outcomes like stature and overweight, and between the timing of sexual maturation and health risk behaviours like alcohol drinking and cigarette smoking. Before findings are presented and discussed, I have outlined some theoretical and empirical considerations which hopefully will provide a broader understanding of this research.

1.1 Theoretical approaches

Pubertal maturation denotes sexual maturation and therefore also the transition to the reproductive phase of life. In many societies, puberty is emphasised by rites of passage that may help the adolescents to redefine their roles and clarify expectations. In our part of the world puberty is considered a private event, but the way the adolescents will cope with pubertal changes (and the new identities) will vary and depend on both individual and contextual factors[2]. Understanding how individuals navigate developmental transitions may be viewed as the crux of understanding risk and resilience across the life span[7]. The co-occurrence of biological, psychological and social changes in puberty, however, is one of the most intricate challenges in research on pubertal maturation and thus, there is a need for comprehensive perspectives, facilitated by interdisciplinary and integrative theories[1;2;7-9].

Individual courses of development may be examined under the framework of turning points in development, i.e. transitional periods or events that have the potential to alter behaviour, emotion, cognition, or context, all of which could result in lifelong change[7]. Transitions have been distinguished from life events in that transitions require reorganisation at the structural or functional level. Individual differences in the experience or negotiation of a transition are associated with a variety of conditions, including development before the transition, the timing of transition for an individual, the individual's experience of the transition and the context in which the transition occurs[7]. Transitions may affect several behaviours, potentially in multiple directions. For example, adolescents that graduate from middle school may generally improve their school adjustment, but may simultaneously start to drink more alcohol, than those still in middle school, since high school attendance provides a context for this behaviour.

Integrative approaches involve pubertal onset, not just as a biological event, but also as an event of social and interpersonal ramifications[1]. Such studies have, for instance, recognised that the developmental impact of hormonal changes on behaviour and emotion are partly mediated by the responses of others in the social environment[10]. This research has also emphasised the timing of puberty relative to one's peer group rather than the onset of puberty per se. Two models have typically been used to test timing effects across these domains; 1) *the stage termination hypothesis* and 2) *the deviance hypothesis*. The first model proposed that individuals' responses to a transition are dependent on the level of biological and psychological development attained before the transition[11]. In case of the stage termination hypothesis, experiencing a transition earlier than others, constitutes a potential risk for unhealthy navigation of the transition, as the individual has less time than most children or adolescents to develop the skills needed to navigate successfully. Alternatively, in case of the deviance hypothesis[2], timing effects are based on the meaning a transition has within a social context. In terms of social processes, being early or late could have negative effects on the individual since she or he may perceive to be deviating from normative development.

From a medical perspective, puberty usually refers to the gradual biological changes that ultimately lead to reproductive maturity. However, both the timing and the tempo of the developmental transition may influence health outcomes (of that transition). Within an epidemiological framework, boys' and girls' timing of sexual maturation (SM timing) may be considered an exposure which antecedent individual risk or protection through biological, psychological and/or social processes. In that perspective, developmental transition may be considered a function of risk and protective factors[1;12;13]. In this thesis I have attempted to combine integrative theories with knowledge from both social and medical sciences to explore the potency of SM timing.

1.2 Pubertal timing

A peculiarity of sexual maturation in the human species is the great variation in age at onset of puberty that is observed among normal individuals despite relatively similar life conditions[14]. For example, girls begin puberty as early as age 8 years or as late as 13 years. Boys begin puberty about 1.5–2 years later than girls, usually between 9.5 and 13.5 years[15;16]. The duration of puberty reflects its tempo or rate of change, ranges from 1.5–6 years, and averages 4 years, but the duration of puberty depends on the timing of its onset and the earlier the onset, the longer its duration[17-19]. Individual differences in the timing and tempo of pubertal development are influenced by both genes and environment. Twin studies have converged on the conclusion that genotypic effects account for 50-80% of the variation in age at menarche and that the remaining variance is attributable to non-shared environmental effects[3]. It is, however, likely that a cascade of genes may determine variations in timing of pubertal onset[14].

Although puberty solely refers to the biological changes needed for sexual maturation (i.e. from the Latin "pubescere" which means growing hairy), it is commonly used to characterise other changes as well. Nonetheless, it is important to note that biological changes not necessarily provide maturation in other areas, and that cognitive and psychosocial development require entirely different timelines[9]. Since adolescents enter and complete their biological changes at different times, their preparation for, and experiences with, the physical changes of adolescence, are highly variable as well.

While *pubertal timing* is a relative measure involving whether individuals' physical development is early, on time (intermediate) or late, compared with same aged and gender peers, *pubertal status* refers to the current degree of physical maturation that individuals have reached with no necessary reference to age[11]. In settings where medical examination has been available, assessments of changes in secondary sexual characteristics (i.e. genital, breast and pubic hair development) has been used following the

criteria proposed by Tanner[15;16], dividing puberty into 5 phases, i.e. from late pre-puberty to late puberty. When such examinations have not been feasible, self-reports have often been used.

Subjective perceptions of being early, on time or late; i.e. perceived pubertal timing, do not only incorporate biological changes, but also psychosocial aspects of maturation and are typically influenced by others, in where the particular peer group may serve as reference[20]. Thus, two individuals who are equally physically matured may perceive themselves as "on time" or "off time" depending on the level of maturation of the adolescents they usually associate with. Given the inevitable social comparisons, perceptions of pubertal timing may be considered more important for psychosocial functioning than the actual pubertal status[21].

The difference between medical and social science markers of puberty may have to do with that physical changes are observed by the child[21]. Not only do they observe these changes in themselves, but they also observe these changes in their peers. In this thesis, several markers of puberty have been utilised.

1.3 Biological changes

Growth and maturation has been considered "a mirror of the conditions in society" and thus, extensively used as indicators of health and hygiene[22]. In Europe, research has been conducted on these issues since the beginning of the 19th century. In Norway, physical growth and maturation of schoolchildren has been systematically registered since 1918 in Oslo[23], but not in the other parts of the country. These data have been frequently used and referred to in the international literature.

1.3.1 Sexual maturation and growth

The most obvious physical signs of puberty are the changes in body fat distribution, the dramatic growth spurt and the occurrence and development of secondary sexual characteristics. Although the primary

mechanism is still unclear, the onset of puberty is believed to occur as a consequence of a change in the hypothalamic-pituary-gonadal axis (HPG)[24], resulting in a dramatic increase in testosterone in boys and oestradiol in girls. Puberty, however, consists of two distinct processes, i.e. increased secretion of adrenal androgens, known as adrenarche, which normally occurs 1-2 years before the maturation of gonadal function, known as gonadarche[3;14]. Both processes contribute to observable bodily changes.

Puberty is associated with significant changes in body composition[25]. Girls tend to accumulate more fat than boys[26]. Fat gain occurs in boys and girls in early adolescence, but then ceases and even reverses temporarily in boys, but continues throughout adolescence in girls. Menarche usually occurs shortly (1-2 years) after the peak height velocity (mean age 11.6 years)[27], ensuring that girls are close to final height before they become fertile. The rise in serum oestradiol relates temporally to breast enlargement, widening of hips, and an increase in body fat. In boys, the growth spurt starts about 1 year after the first enlargement of testes (11 years) and boys reach peak height velocity about two years after girls, i.e. at an average age of 13.5 years[27]. As height velocity decelerates in boys there is acceleration in fat gain. Lean body mass, however, increases rapidly during adolescence to reach a maximum at 20 years. The rise in testosterone with its strong anabolic properties coincides with the rise in lean body mass[28;29]

The pubertal growth spurt is influenced by a number of factors such as hormones, nutrition, physical activity and general health, acting in concert in order to modify the genetic potential for growth[25]. Normal pubertal growth is primarily orchestrated through the action of growth hormone (GH) and insulin-like growth factors (IGF). During puberty, elevated sex steroid concentrations (especially oestrogens) stimulate GH production, leading to an activation of the whole GH/IGF-1 axis. Interactions between GH and sex steroids (especially androgens) express anabolic effects on muscle mass, bone mineralization, and body proportion which constitute the male and female adult body composition[28]. The pubertal growth spurt contributes largely to adult height, about 30 cm in boys and 25 cm in girls, but with great

variation between individuals and within groups[15;16]. Regulation of linear growth may not be similar for boys and girls, and the relative contribution of different growth phases in childhood and puberty may also vary between genders[19]. Pre-pubertal intensity of growth, seems to determine adult size to a high degree, but more in boys than in girls[19].

Some studies have suggested that early maturation is associated with shorter final height, but most of the reported differences have been small[30-33] or absent[17;34-37]. Early sexual maturation and shortness has previously been attributed to attenuated growth in childhood and adolescence, possibly explained by lower genetic growth potential, or because of impaired intrauterine growth[38-42].

1.3.1.1 Secular and current changes in height, weight and maturation

During the past two centuries a striking change in height, weight and SM timing has been observed in all countries in Europe, but changes have not occurred simultaneously in all countries[43;44]. In the literature, this phenomenon is termed secular trends, which may lead to the misconception that there has been a continuing change in one direction. Due to the large variation in pubertal timing between countries and ethnic groups, both geographical, socio-economical and ethnic factors should be considered to allow a meaningful interpretation of secular or current shifts in the timing or tempo of sexual maturation[14]. In Europe, for example, there is a distinct north-south gradient, where girls in France and the Mediterranean countries start to menstruate relatively earlier[14].

Secular changes towards taller stature, heavier body weight and earlier maturation are predominantly linked to improvements in nutrition and health[22;43;45]. In times of food scarcity and starvation, girls tend to begin menstruation much later. Improved nutrition in the last 150 years has led to a gradual drop in AAM to the point that “over-nutrition” (creating the childhood obesity epidemic) may be putting even more

downward pressure on AAM. In societies in which there are substantial differences between social classes in nutritional and health status, e.g. during periods of socio-economic instability, girls from higher social classes experience earlier pubertal development than do girls from lower social classes[44]. The secular change has been most intense within lower SES groups, where living conditions have improved most dramatically over time. Recent decline of mean AAM in many countries is suggested to be a consequence of the decreasing number of late maturing girls[43]. In Norway (Oslo), mean age at menarche (13.3 years) was practically unchanged from 1950 to 1980-1985[23].

Whereas AAM reference data seem to have stabilised in most industrialised countries during the 1990s[44], two American studies (PROS)[46;47] highlighted an unexpected and unexplained advance in physiological age at the onset of puberty. These studies indicated that the initial signs of puberty, i.e. breast buds and pubic hair, are showing up earlier than the age that paediatricians long believed was the threshold of normal puberty in both genders. According to the PROS studies (Pediatric Research in Office Settings), it was suggested that the entire population of girls has shifted to about 1 year earlier development than it was in the 1960s, but with no clear corresponding decrease in AAM. It was questioned whether these results could reflect the high prevalence of obesity in US children, and that obesity promotes earlier onset of breast development, but not the progression of puberty through later pubertal stages[48-50].

The possible dissociation between the timing of pubertal events in the US, however, appears to be contradictory to observations of an acceleration of the progression or tempo of pubertal maturation and growth[43;44]. For example, adult height is reached at an earlier age[43;45]. Critical analyses of these and other studies, however, highlighted the methodological difficulties that may contribute to contradictory and inconsistent observations[48;51-53]. More recent studies from the US and Europe have shown that although AAM has stabilised in some countries, there is still evidence of profound socioeconomic effects

on AAM[54;55]. The large EPIC study (European Prospective Investigation into Cancer and Nutrition), that includes 286,205 women from 9 countries reported in 2005 that mean AAM had decreased by 44 days per 5-year birth cohort, varying from 18 days in the UK to 58 days in Spain and Germany[56].

A shorter duration of growth and maturation could theoretically cause less pubertal height gain, but most studies have indicated that the shorter growth period is compensated by an accelerated growth rate before puberty and thus, of little or no relevance for final height[17;36;37;57]. Most of the secular increase in height that is seen in European adults during the same period (1990-2000), is suggested to be obtained in early infancy or childhood[45;58;59]. According to the EPIC study, women had grown 0.29 cm taller per 5 year birth cohort, varying from 0.42 cm in Italy to 0.98 cm in Denmark. This study also showed that more recent birth cohorts had their menarche earlier and grew taller than older birth cohorts[56].

1.3.1.2 What are putting some children on a faster road to sexual maturity?

Many factors may explain the secular or current change in timing and progression of puberty. For example, early or precocious puberty is more prevalent among children adopted from developing countries, and studies on migrant children have suggested that the peri-pubertal period may be exquisitely sensitive to reprogramming[51]. However, other factors also need to be taken into consideration, including the possibility that endocrine disruptors could trigger pubertal development[14]. Exposure to chemicals that have oestrogenic or anti-androgenic properties has been associated with precocious puberty in children; hair care products, cosmetics and ointments are among those items to blame[51;60;61]. Some variations in AAM can be related to low or high birth weight[39-41;62;63], but also climatic conditions, such as temperature and light-darkness rhythms influenced by geography and seasons, may modulate the reproductive axis, perhaps explaining the south–north gradient in menarcheal age around the world[14]. Childhood over-nutrition, however, is suggested to represent the single most important environmental factor with profound effects on the tempo of growth and maturation[51;64]. The US NHANES II study showed that the frequency of early menarche was closely linked to obesity status: 33% of

higher-weight girls (above the 95th percentile) attained menarche before age 11, compared to 13% of lower-weight girls[65].

1.3.2 Childhood nutrition and pubertal growth trajectories

Obesity is a major public health problem that has grown to epidemic proportions throughout the world[66]. Ten percent of the world's school aged children and about 20 percent of European children are estimated to be carrying excess body fat with increased risk of developing chronic diseases[67-69]. Since the problem increases so rapidly, the health consequences of overweight in childhood will only be fully apparent in the next decade or so. Among the most common sequelae of childhood obesity are hypertension and dyslipedemia, with increased risk of coronary heart disease, type II diabetes, respiratory problems, and other chronic diseases[31;70-76]. Overweight and obesity may also be considered a burden that results in psychosocial problems[20;77-79] and certainly in a reduced capacity for physical activity[80]. Since 85% of obese youngsters will become obese adults, the co-morbidity exerts an important toll on industrialised societies[68]. The risk is even higher in children with obese parents[81], owing both to genetic influences and to the shared environment (i.e. nutritional status, lifestyle, food preferences).

Although cultural, environmental and genetic factors play a role, overweight and obesity are not restricted to a single ethnic, age or socio-economic group[82]. The environmental factors may include sedentary activities, low physical activity, and a shift in diet towards more fast foods with high fat, refined carbohydrates and high calorie content. Among genetic factors, polymorphisms or mutations in leptin (i.e. protein product of the obesity gene) and leptin receptors may be involved in the pathophysiology of obesity[83].

The extent and severity of the overweight epidemic has refocused interest on the natural history of disease. Several critical periods in childhood have been identified in the development and persistence of

obesity[6]. In the gestational period, there is a direct association of high birth weight with subsequent adiposity. Another critical period is ages of 5-8 years, where adiposity rebound may serve as an index of further obesity[81], and the final risk period for the development of persistent obesity is adolescence[6].

It is well established that overweight children tend to mature earlier than their leaner counterparts although the mechanisms are unclear[36;63;84;85]. That early maturation is associated with excess adiposity reflects the more general phenomenon that childhood obesity is auxogenic: some of the excess calories responsible for increased fatness are also reflected in accelerated growth and maturation. For this reason, obese children characteristically have accelerated growth, and in early pubertal stages obese children show advanced height and bone age and tend to reach sexual maturity earlier[32;36;40;86]. Whether this phenomenon is the result of the direct effect of adipose tissue (critical weight–menarche hypothesis), as proposed by Frisch and Revelle, or is secondary to overall skeletal maturity, remains unclear[87;88]. Growth potency associated with body fatness, however, may be restricted to certain ages in early life and possibly linked to accelerated weight gain during infancy or childhood[40;51;89-91]. Freedman *et al,* found that differences in adult obesity that could be attributed to childhood growth and tall stature, were already established before puberty, i.e. in children younger than 9 years, and not later[92].

In recent research the influence of leptin has received much attention. Since obese children have high leptin levels, this hormone is suggested to have a permissive effect on the pubertal process and pubertal growth[83]. Leptin is secreted mainly from white adipose tissue, and has been shown to be inversely related to age at menarche[93]. Apparently there is a critical concentration of leptin for the timing of menarche. Leptin is suggested to be the signal that transmits the information to the brain that fat stores are adequate to cover the energy requirements of reproduction. Therefore, leptin may participate in the timing of puberty, without necessarily being a trigger for onset of puberty. It may rather serve as a metabolic “gate” for puberty to progress[83;94]. In boys, there is a pre-pubertal peak of serum leptin levels

preceding the rise of free testosterone, growth hormone (GH) and insulin growth factor (IGF-1). About 3 years after the rise in serum testosterone levels, leptin levels fall to baseline concentrations. In girls, however, leptin levels rise throughout puberty, concomitant with the rise in oestrogen levels even after correction for body weight and fat mass[95].

Some authors have suggested that the inverse relation between AAM and adult overweight could be attributed to childhood over nutrition rather than early maturation, but it has been difficult to isolate the influence of early adiposity from the effects of early maturation[31;96;97], and most studies have reported averaged results[30;98-103]. Limited research has been conducted on boys, which may be due to the difficulties of measuring sexual maturation in large epidemiological studies.

1.4 Psychosocial changes

The adolescent transition is not only characterised by changing bodies, but a range of psychological and social challenges that may account for a significant increase in health damaging behaviours. Thus, research on the role of pubertal maturation for psychosocial adjustment and behaviours received interest as early as the 1930s[2]. Most of the scientific work conducted within this field has been carried out by sociologists and psychologists.

1.4.1 Risk behaviour involvement

Alcohol and tobacco use are the most commonly used substances among adolescents, also characterised as health damaging behaviours. For young adolescents, however, experimenting with these substances may be perceived as anticipation of adult life, connoting adult status[9]. Absence of health risk behaviours is therefore not equivalent to health and well being, and experimentation does not necessarily lead to maladjustment[104;105].

1.4.1.1 Alcohol drinking

Adolescent experimentation with alcohol is widely regarded as a normal part of adolescent development without adverse consequences. This is consistent with the high prevalence of alcohol use among adolescents and the apparently low prevalence of manifest alcohol related disorders. On the other hand, early drinking appears to increase the risk of progression to problem use[4;106;107]. Studies have generally shown substantial stability in more risky drinking over time [4;106-110]. Acute alcohol poisoning is greatly under-recognised and yet the most common cause of substance-related death[111;112]. Young people who are intoxicated will be cognitively impaired and will not be able to judge situations as dangerous. Intoxication may, through a direct effect on behaviour, give rise to accidents, burns, falls, injuries and drowning, social conflicts, sexually transmitted diseases and unwanted pregnancy[113;114]. Recent research may indicate that there are only minor differences in alcohol drinking across socio-demographic subgroups, defined by geographical region, population density, parental education and family structure[115].

The prevalence of alcohol use and drunkenness increases sharply during adolescence and the problem is substantially greater among 13th graders than among 8th graders. Nevertheless, a considerable proportion of 8th graders already use alcohol. In Norway, as in other Northern European countries, national statistics[116] shows there has been a formidable increase in alcohol consumption during the last decade. Among adolescents who report alcohol drinking (15-20 years), the average consumption of pure alcohol has increased from 2.9 litres in 1990 to 4.8 litres in 2005. Two out of three report that they have consumed alcohol during the past 4 weeks, and nearly 70 percent have been drunk at least once during the past 6 months, and the figures are similar for boys and girls. Girls are also about to reach the same intake of alcoholic beverages as boys, which gives rise to concern in several respects.

1.4.1.2 Cigarette smoking

Tobacco use is the leading behavioural cause of death - it roughly doubles the lifetime risk - and it also plays a role in creating health inequalities[117]. Although acute harm is seldom apparent, youths' smoking affects both current well being and long term disease risk. Perhaps most crucial, those who start early also tend to smoke heavily as adults and are least likely to quit[118]. Young smokers have more sick-days and are more prone to stomach pain, headache and tiredness, although such disorders may also reflect emotional and social problems[119;120]. Smoking at least doubles the risk of symptoms such as cough and wheezing and increases the risk of respiratory infections[119;121]. In many developed countries girls are now more likely to smoke than boys. The process of becoming a smoker is complex, but dependence appears to develop rapidly. Early predictors of daily smoking include low parental education, one-parent household, early drinking, high drive for thinness, stress and lower behavioural conduct[122]. Smoking is clearly associated with the use of alcohol and other drugs[118;123]. For example, regular drinking is strongly associated with smoking, and "relief" smoking predicts late heavy drinking. Early smoking in particular appears to predict future substance use, and other health risk behaviours.

1.4.2 Risk taking associated with the timing of puberty

Of special interest in terms of risk taking are adolescents at the extreme end of the pubertal timing continuum: early maturing females and late maturing males[10;11;124-127]. It has been shown that risk behaviour involvement is particularly prevalent in the group of early maturing individuals, especially girls[128-136]. For these adolescents, limited social and cognitive skills are combined with increased needs pertaining to independence, increased heterosexual initiatives, and social networks consisting of older adolescents[126]. These adolescents may feel environmental pressures to behave more like adults, and the social milieu may expect early developers to have skills that they have not yet acquired. They may also be less prepared to cope with emotional changes than their on time and late maturing peers[126;133;134].

It has, however, not been clear if early established drinking and smoking patterns related to pubertal timing persist over time, or if late maturing boys and girls eventually catch up with their earlier counterparts[128;129;132]. It is also unclear if adolescents' subjective perception of their own timing is more important for their behaviour than their actual biological timing[135;137]. Late maturing boys, without the attributes most highly valued by peers (less athletic) may also be particularly prone to engage in risk behaviours, but the results have been inconsistent[138-142]. Also, most previous research in this area has only included information on girls, and there is little knowledge about boys. Most previous studies that have addressed these questions were conducted several decades ago. Since the society and life-styles have changed rapidly over the years[143], as has the social meaning of puberty, the impact of pubertal timing on adolescents' use of substances need to be reconsidered.

2.0 Objectives

Effects of pubertal changes on growth and psychosocial adjustment may be considered from biological (i.e. physiologic or hormonal), psychological (in terms of coping with developmental tasks), social (roles), environmental (societal) or from an interaction point of view. In this thesis, comprehensive perspectives and epidemiological concepts, and methods were applied to study the influence of boys' and girls' timing of sexual maturation (SM timing) on different health outcomes.

More specifically, the aims of the thesis are:

1. To estimate the prevalence of advanced (risky) alcohol drinking and cigarette smoking in late adolescence related to SM timing and gender (Paper I).
2. To study whether perceptions of being early, on time or late matured relative to same aged peers were associated with the prevalence of alcohol drinking and cigarette smoking, and also to study the influence of pubertal status on this association (Paper II)
3. To study the association between SM timing and overweight in late adolescence and whether this association could be modified by level of central adiposity as assessed in early adolescence (Paper III)
4. To study whether the association between SM timing and height, and height gain during adolescence could be modified by level of central adiposity as assessed in early adolescence (Paper IV)

3.0 Materials and methods

3.1 The Young HUNT study

The Young HUNT 1 study was conducted between August 1995 and June 1997, and the Young HUNT 2 study, conducted between January 2000 and June 2001, in Nord-Trøndelag county in Norway[144]. The Young HUNT 1 (baseline) constitutes the adolescent part of the Nord-Trøndelag Health Study (HUNT 2) in which all inhabitants 13 years or older were invited to participate. The Young HUNT 2 study (follow-up) took place about four years later, comprising all students in 12th or 13th grade in high school (aged 16-20 years).

The HUNT Research Centre, located in Verdal in Nord-Trøndelag, with Associate Professor Turid Lingaas Holmen as the Young HUNT project manager, was responsible for the planning, administration and implementation of the Young HUNT 1 and 2 studies. Institutional project collaborators were the National Institute of Public Health (Oslo), the Nord-Trøndelag University College (Levanger), the University of Science and Technology (NTNU, Trondheim) and Levanger Hospital (Levanger). HUNT Research Centre has since 2001 been an integral part of the Faculty of Medicine at the Norwegian University of Technology and Science (NTNU), and responsible for the administration and delivery of data from the HUNT database to research projects.

The Young HUNT study was funded by financial support from the Norwegian Ministry of Social and Health Affairs, the Norwegian Research Council, Nord-Trøndelag County Council, the Norwegian University of Science and Technology (NTNU), the National Institute of Public Health, the Norwegian Women's Public Health Association and Astra Zeneca AS. This doctoral work has been funded by the Norwegian Research Council as a research fellowship and financial support from the Nord-Trøndelag University College and the Norwegian University of Science and Technology.

3.1.1 Demographics

Nord-Trøndelag County is situated in the middle part of Norway (18 counties) and the total number of inhabitants was 128,694 in January 2006, of whom 12,818 (10%) were between 13 and 19 years of age. The population has been stable, but due to some immigration, the number of inhabitants has increased slightly over the last decades. The geographic, demographic and occupational structure is fairly representative for Norway as a whole. The county has coast and inland areas, characterised by rural areas and small towns, but it lacks densely populated areas and larger cities with more than 50.000 inhabitants.

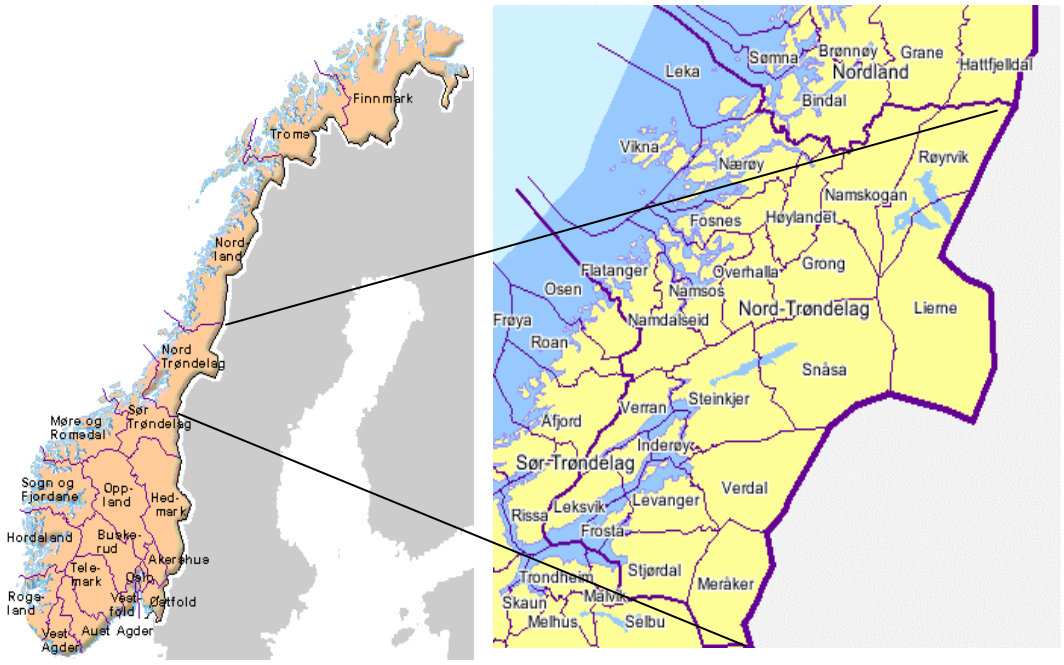

Figure 1. Study area, the Nord-Trøndelag County of Norway (www.norge.no)

3.1.2 Ethics

The Young HUNT study was approved by the Regional committee for ethics in medical research, and by the Norwegian Data Inspectorate. Also school authorities in the county and all principals at all middle- and high schools approved that the Young HUNT study was carried out. Each student signed a written consent to participate in the study. The consent informed the student about future use of data and their rights for protection of privacy. This information along with more general information was also distributed to the adolescents ahead of the study to be discussed with parents or superiors. Superiors of students younger than 16 years also gave their written consent.

3.1.3 Data collection

The data collection included a questionnaire, a physical examination and an interview.
Questionnaire: A self-administered questionnaire (Appendix I) was completed during one lesson in a setting with no opportunity to observe the answers of others, monitored by a teacher. The questionnaire was identified by a bar code of the unique 11-digit registration number given to all Norwegians at birth. After completion, each student put their questionnaire into a blank envelope and sealed it. Field workers collected the envelopes. The questionnaire included a broad range of topics related to health and health related behaviours. *Clinical assessments:* Within a month after completing the questionnaire the students underwent clinical examinations, conducted by trained project nurses in confidential settings located at each school. Height, weight, hip and waist circumference, blood pressure and lung function were measured. All clinical assessments were standardised according to written procedures. *Interview:* Two structured interviews were conducted by the project nurses, but these interviews are of no relevance for this thesis.

3.1.4 Quality control

All field workers were trained in techniques and equipment by the project leader before they started their field work. To ensure procedures, concurrent evaluation was performed by regular meetings and

telephone contact between the project administration and the field nurses during the entire data collection period. Standardised control routines were also followed after data were collected and in connection with punching of data.

3.1.5 Participation

The target group for the Young HUNT 1 study was all inhabitants in Nord-Trøndelag County aged 13-19 years during 1995-1997[145] (www.hunt.no). Since adolescents usually graduate from high school the calendar year they reach 19 years of age, about half of those who were 19 had already left school and were not invited (flow-chart, page 30). 126 students in middle school and 40 students in high school were respectively 12 and 20 years of age when they participated in the Young HUNT 1 study. In total, 9917 adolescents were invited to the survey, of whom 8950 (90%) completed the questionnaire; 4485 boys and 4465 girls. The Young HUNT 2 study (follow-up) was conducted as a cross-sectional health survey, comprising all students in 12th and 13th grade in high school[144]. Of the 4743 students in middle school who participated in the first Young HUNT study, 2969 students were eligible for participation. Of these adolescents, a total of 2399 (81%) completed the questionnaire.

Since the surveys were conducted in schools, the main source for invitations was the class lists of students registered at each school. Adolescents with apprenticeship contracts and those who had quit school were to some extent registered by superior school authorities, but since they were not registered systematically, these lists were incomplete. In order to reach those who were registered, invitations and questionnaires were sent by mail to private addresses, but participation was generally low in these groups.

Relatively more students attended academic study lines than vocational study lines. Thus, students from vocational study lines represent 35 % of the boys and 29 % of the girls in the study cohort. More girls

than boys attended academic study lines, and this may explain why more girls (53%) than boys (47%) participated at follow-up in high school.

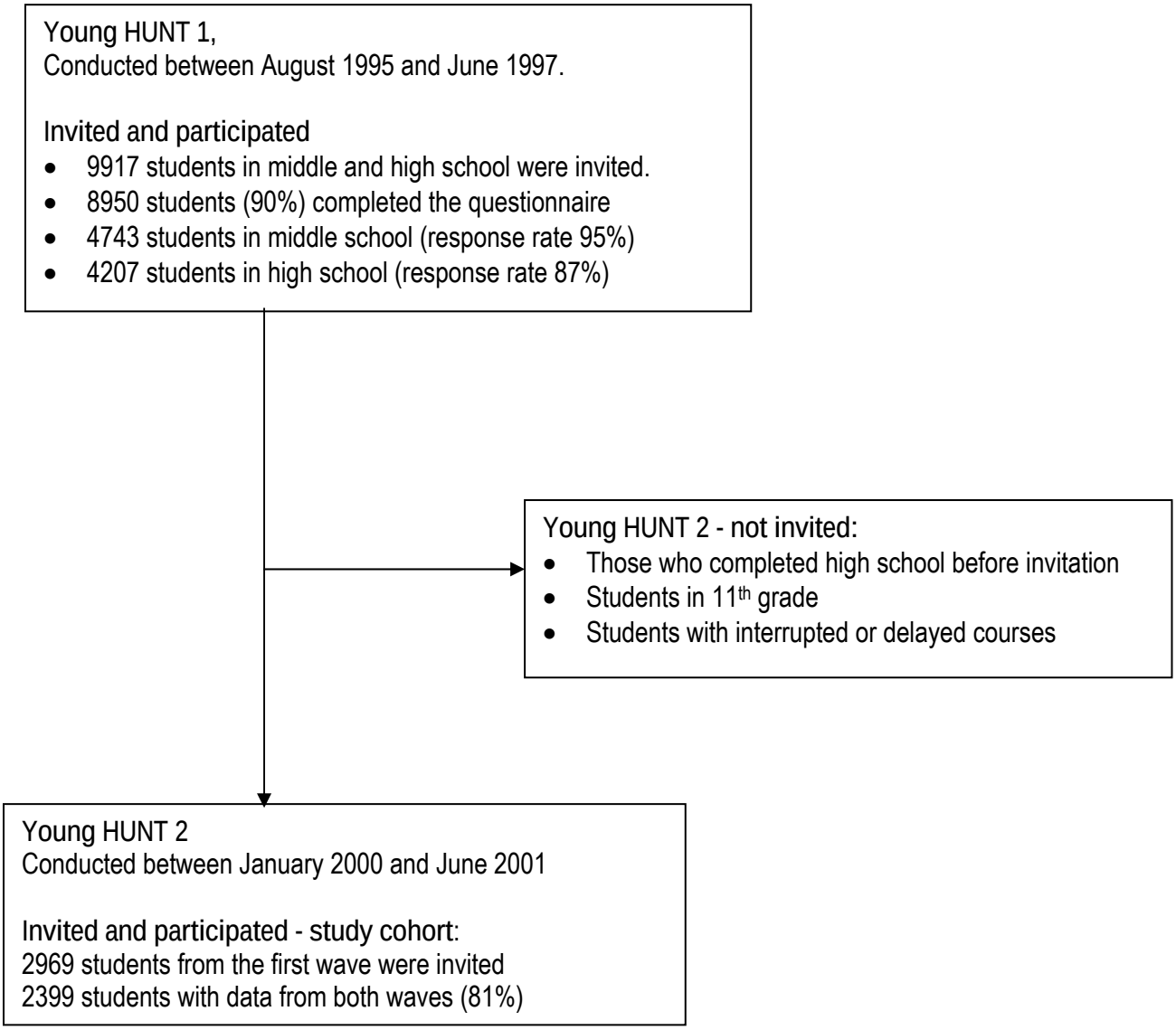

Figure 2. Flow-chart participation and attrition from Young-HUNT 1 to Young HUNT 2.

3.2 Material used in Paper I-IV

The study cohort described in Paper I (prospective data) included 2129 boys and girls with questionnaire data from both Young HUNT studies, and with adequate data on both SM timing and substance use. The study population described in Paper II (cross-sectional data) included all 8950 students attending middle or high schools with questionnaire data. The study cohort described in Paper III and IV (prospective data) included 1605 boys and girls with adequate baseline information on both SM timing and anthropometry from both Young HUNT studies.

3.2.1 Data from other sources

In Paper IV, we combined data from the Young HUNT 1 and 2 surveys with birth data from the Medical Birth Registry and parental data from the HUNT 2 study. The adult part of the HUNT studies, the Nord-Trøndelag Health Study (HUNT 2) was conducted during 1995-97, and all inhabitants 20 years or older were invited[145]. Of the 92,936 individuals eligible for participation, 66,140 persons (71.2%) took part in the survey (www.hunt.no). All information from the HUNT studies was identified by a bar code of the 11- digit unique personal number given to all Norwegians at birth. Statistics Norway matched the HUNT data files with public registry data and returned the matched data material with encrypted ID codes to secure anonymity. Among data provided by the Statistics Norway were information on familial relationships and demographic information.

3.3 Variables used in paper I-IV

Questions are shown in Appendix I.

3.3.1 Measuring puberty and the timing of pubertal changes

In this thesis, SM timing in boys was indicated by pubertal status (Paper I-IV), and by perceived pubertal timing (Paper II). In girls, SM timing was indicated by pubertal status (Paper I and II), age at menarche (Paper III and IV) and perceived pubertal timing (Paper II).

In the Young HUNT (95-97) questionnaire, participants were asked to assess changes in their secondary sexual characteristics by use of the Pubertal Developmental Scale (PDS)[146;147]. All participants rated themselves according to growth spurt and pubic hair growth; girls were asked about menarche and breast development, and boys were asked to assess changes in voice and facial hair growth. Among the five gender specific questions in the original PDS, one of the questions (about skin changes) was not included in our questionnaire. Assessments of skin changes have, however, been less reliably reported compared to other maturational characteristics[147;148]. SM timing was classified according to age and gender specific distribution of pubertal status in both boys and girls. Those with PDS- score in the lowest quintile of the distribution were classified as “late”, and those within the highest quintile as “early”. Participants from the 20th to 80th percentile were classified as “on time” (Paper I and II) or “intermediate” (Paper III and IV).

Mean AAM in this study population was 13.2 years, similar to most studies conducted in girls from North European countries[23;50;58]. Girls were asked to denote their age at menarche in both years and months. At baseline, one fifth of the responders had not yet reached menarche (n=158), or had incomplete or missing data (n=30). For these girls we relied on information on age at menarche collected at follow-up. We classified girls in the lowest quintile of age at menarche (<12.5 years) as “early” matured and girls in

the highest quintile (≥14.0 years) as “late” matured. Girls with age at menarche between 12.5-13.9 years were classified as “intermediate” (Paper III-IV).

The questionnaire contained a scale measure of perceived pubertal timing (Paper II), as recommended and validated by Dubas *et al*[137], where the students were asked to assess their level of physical maturity relative to same-aged peers. The original validated scale consisted of five response categories, whereas our scale as previously used in a previous Norwegian study, consisted of seven[149]. We classified those who answered much earlier, somewhat earlier or a little earlier as “earlier” (31%), those who answered just like others as “on-time” (51%); and those who answered little, somewhat or much later were classified as “later” (18%).

3.3.2 Measurements and classification of anthropometry

Clinical assessments of height, weight, waist and hip circumference were performed in both Young HUNT surveys. Height and waist and hip circumference were read to the nearest centimetre (cm), and weight to the nearest half kilogram (kg). The students wore light clothes and no shoes.

Body-mass index (BMI) and overweight were used as outcome variables in Paper III. BMI was calculated as weight in kilograms divided by the squared value of height in meters (kg/m^2). Overweight was classified according to the International Obesity Task Force (IOTF) standards, which link BMI percentiles during childhood and adolescence to the widely used adult cut-off-points of 25 kg/m^2 as a definition of overweight[150].

Waist circumference as assessed in early adolescence (baseline) was used as exposure and indicator of level of central adiposity (Paper III and IV). Boys and girls with waist circumference above the median for their half-year-age-group and gender were classified as having “high waist”, and those who were below or at the median value were classified as with “low waist”.

3.3.3 Measuring alcohol and tobacco use.

Questions about alcohol use were taken from the Norwegian part of the European Cross-National Health Behavior in School-Aged Children survey (HBSC), conducted repeatedly as a WHO Collaborative Study[151]. Students were asked if they had ever drunk alcohol, and if yes, how many times they had been drunk. In the Young HUNT 2 survey, another modified question about the frequency of alcohol drinking was adopted from the HBSC questionnaire. By the use of a quantity–frequency (Q-F) question, adolescents were also asked to report the amount of beer, wine and spirits, they usually consumed during a period of two weeks, and on the basis of these data the total amount of alcoholic beverages was calculated and transformed into litres of pure alcohol a year. Reliability and validity of self-reported alcohol consumption by adolescents has been shown to increase when questions regarding specific beverage types and quantity are asked, as in our study[152].

Since alcohol drinking is so common and increases dramatically with age, definitions of more risky drinking are crucial. In an attempt to take some of this variation into account, we classified risky drinking 1) according to the distribution of drinking by grade in school and gender in this particular study population, and 2) by combining information of drunkenness, frequency of drinking and alcohol consumption into one composite outcome variable called “advanced drinking”. In Paper I, students who had 1) been drunk more than 10 times, 2) used to drink alcohol at least every second week or more often, and 3) simultaneously reported relatively high alcohol consumption (above the 70th percentile, estimated for boys and girls separately), were classified as “advanced drinkers”. In the cross-sectional study (Paper II), advanced drinking was classified according to the distribution of drunkenness and alcohol consumption by grade in school and gender. Definitions and classifications are described in more detail in Paper I and II.

Information on cigarette smoking was obtained by three questions. Current smokers were identified as those who answered “yes” to ever smoking (at least one cigarette) in combination with responding “yes, I smoke daily” or “yes, I smoke occasionally” to the question “Do you smoke now?” Participants, who had never smoked cigarettes or had stopped smoking, were classified as non-smokers.

3.3.4 Covariates

Definitions and classification of potential confounding factors like parental level of education, parental drinking and smoking habits, parental marital status, leisure time physical activity, dietary sugar intake are described in more detail in Appendix II.

3.4 Study design

The papers included in this thesis were conducted within an epidemiological framework, comprising one descriptive cross-sectional study (Paper II) and three prospective studies (Paper I, III and IV).
A prospective study cohort is characterised by a group of individuals selected from a defined population and followed over time to identify risk (disease) or resilience (health) between persons classified as exposed or not exposed. The Young HUNT 1 (baseline) and The Young HUNT 2 (follow-up) surveys made it possible to conduct longitudinal studies, following adolescents from all 24 municipalities in Nord-Trøndelag county from early to late adolescence. Nord-Trøndelag constitutes one out of 18 counties in Norway. In Paper I-IV boys’ and girls’ SM timing, as assessed at baseline in early adolescence, was defined as exposure variable, presuming that the timing of pubertal changes is vital not only for bodily changes, linear growth and stature, but also for the initiation and advancement in alcohol drinking and smoking during adolescence. Since the relation between the timing and health outcomes was suggested to be influenced by other bio-psycho-social factors, possible confounding factors available in this material or in supplementary materials, were taken into account in the analyses. To test the hypotheses under study, the timing of sexual maturation was considered the main exposure, but in Paper III and IV, the combined exposure of SM timing and level of central adiposity was examined.

3.5 Statistical methods

In this thesis, descriptive statistics as well as multivariate logistic regression modelling (Paper I, II and III) and general linear modelling (Paper III and IV) were applied to study the associations between exposure and outcomes. Our goal with the modelling was to obtain a valid estimate for the exposure-outcome association and not prediction. The multivariate analytic tools gave us the opportunity to include and control for potential confounding variables, and to test for possible effect modification.

Confounding or effect modification The rationale for assessing confounding should primarily be based on theoretical or empirical considerations[153]. Since confounding is a validity issue, which addresses systematic error rather than random error, the assessment of confounding was carried out without using statistical tests. Effect-measure modification differs from confounding in several ways. Whereas confounding is a bias that investigators try to disentangle from the effect estimate, effect-measure modification is a property of the effect under study. Thus, it is an effect to be reported rather than a bias to be avoided. In epidemiological analysis one tries to eliminate confounding, but tries to detect and estimate effect-measure modification.

Logistic regression analyses were performed to estimate the association between the exposure (SM timing) and different health outcomes. Logistic regression modelling is commonly used when the independent variables include both categorical and numerical variables, and the dependent variable is binary (dichotomised). Logistic regression requires no assumptions of the independent variables, but there are some statistical issues that need attention, i.e. multicollinearity, multiple testing and influential observations[154]. The regression coefficient, odds ratio (OR) expressed the likelihood of early or late matured individuals to drink or smoke (Paper I and II) or to be overweight (Paper III), compared to on time/ intermediate counterparts. All analyses were performed separately for boys and girls, and adjusted for age. Interactions between pubertal status and perceived pubertal timing and outcomes in Paper II

were tested by inclusion of the interaction term in the model and by stratification. In Paper I and II, the potential confounding of age, parental level of education, parental drinking and smoking, and parental divorce on outcomes were tested, and in Paper III the potential confounding of age, waist circumference, parental level of education, dietary sugar intake and leisure-time physical activity were tested.

General linear modelling (GLM) provides regression analysis and analysis of variance for one dependent variable by one or more independent variables. GLM variance analyses were used to estimate means and mean differences in BMI (Paper III), and height and height gain (Paper IV) between individuals classified as early, intermediate or late sexually matured and by level of central adiposity. All analyses were performed separately for boys and girls, and adjusted for age. Interactions between factors, and the potential modifying effect of level of central adiposity on the association between pubertal timing and outcomes were tested by inclusion of the interaction term in the model and by stratification. In Paper III, the potential confounding of age, parental level of education, dietary sugar intake and leisure-time physical activity on outcomes were tested, and in Paper IV the potential confounding of birth length, mid-parental height and parental level of education on outcomes were tested.

4.0 Review of Papers I-IV

Review of Paper I

Sexual maturation in early adolescence and alcohol drinking and cigarette smoking in late adolescence: a prospective study of 2,129 Norwegian girls and boys. *Bratberg GH, Nilsen TI, Holmen TL, Vatten LJ*. Eur.J Pediatr 2005;164:621-5.

Objective: Early sexual maturation has been associated with higher involvement in risk behavior during early and mid adolescence. In a prospective study of 2129 girls and boys, we investigated whether the timing of sexual maturation was associated with cigarette smoking and alcohol drinking in late adolescence, and whether this relation differed between boys and girls. *Methods:* 980 boys and 1149 girls, who participated in a cross-sectional study in middle school, were included in a follow-up study in high school four years later. Self-rating of pubertal status as registered at baseline in middle school, was used to indicate the timing of sexual maturation. Age-adjusted odds ratios (OR) with 95% confidence intervals (CI), estimated by logistic regression, were used to assess the association between sexual maturation and alcohol drinking and daily smoking at follow-up. *Results:* We found that girls who had matured early (OR 1.7, CI 1.2-2.4) or late (OR, 1.5, CI, 1.1-2.2) were both more likely to report more advanced drinking in late adolescence, compared to girls who were on time. Boys who had matured late, were less likely (OR 0.5, CI 0.3-0.8) than boys who were on time to engage in advanced drinking. In general, daily smoking was more common among girls than boys, and more common among girls who had matured early (OR 1.5, CI 1.1-2.2), compared to girls who were on time. Adjustment for social factors, e.g. parental education and marital status and parental drinking and smoking habits, did not substantially influence these results. *Conclusion:* For girls, but not for boys, early sexual maturation was associated with more advanced drinking and higher frequency of smoking in late adolescence. In boys, late sexual maturation was associated with reduced risk of advanced drinking.

Review of Paper II

Perceived pubertal timing, pubertal status and the prevalence of alcohol drinking and cigarette smoking in early and late adolescence: *a population based study of 8950 Norwegian boys and girls. Bratberg GH, Nilsen TIL, Holmen TL, Vatten LJ*. Acta Paed 2007;96(2):292-5.

Aim: To study whether perceived pubertal timing is related to the prevalence of alcohol drinking and cigarette smoking among adolescent boys and girls. *Methods:* The Young HUNT study (95-97), conducted in Nord-Trøndelag County in Norway, comprises information from 8950 students, aged 13-19 years. Odds ratios (OR) with 95% confidence intervals (CI) related to alcohol drinking and cigarette smoking were estimated by logistic regression analyses. *Results:* Boys and girls who perceived themselves as early matured were more likely to report more risky drinking than those who perceived themselves as being on time, both in middle school and high school. A nearly identical pattern was found for smoking. However, boys in middle school, who perceived themselves as late, were more likely to smoke than those who were on time.

Conclusion: In both genders, perceived early maturation was associated with increased risk behaviour involvement. Perceptions of being early in combination with high pubertal status yielded the highest prevalence of alcohol and tobacco use.

Review of Paper III

Early sexual maturation, central adiposity and subsequent overweight in late adolescence. *A four-year follow-up of 1605 adolescent Norwegian boys and girls: the Young HUNT study.*

Bratberg GH, Nilsen TIL, Holmen TL, Vatten LJ. BMC Public Health 2007,7:54

Background Early sexual maturation has been associated with overweight that may persist after the completion of biological growth and development. We have prospectively examined the influence of early sexual maturation on subsequent overweight in late adolescence and assessed if this association was modified by central adiposity in early adolescence.

Methods 1605 Norwegian adolescents were followed from early (baseline, mean age 14.2 years) to late adolescence (follow-up, mean age 18.2 years). Maturational timing was assessed by self-reports of pubertal status (PDS) in boys and age at menarche (AAM) in girls. Central adiposity was classified according to waist circumference (waist) measured at baseline, using age and gender specific medians as cut off. Overweight was classified according to International Obesity Task Force (IOTF) standards.

Results At follow-up, early sexual maturation in girls, but not in boys, was associated with overweight. This association, however, was restricted to girls with high waist circumference (>median) at baseline (OR, 2.7, 95% CI 1.5-4.9). Thus, age at menarche was not associated with overweight in girls with low waist (≤ median) at baseline. Central adiposity was, independent of maturational timing, associated with higher BMI at follow-up in both genders, but differences were more pronounced among early matured girls (3.5 kg/m²), than among intermediate (2.7 kg/m²) and late matured girls (1.2 kg/m²).

Conclusions

In girls, the combination of central adiposity and early age at menarche appears to increase the risk of being overweight in late adolescence.

Rewiew of Paper IV

Combined influence of early sexual maturation and central adiposity on subsequent stature. A four-year follow-up of 1,605 Norwegian boys and girls: the Young-HUNT study. *Bratberg GH, Nilsen TI, Holmen TL, Vatten LJ.* Eur.J Pediatr 2006;165:787-93

Shorter adult stature has been attributed to early sexual maturation as well as early adiposity, but it is not clear if these factors are interrelated. 1605 Norwegian adolescents were followed from early (baseline) to late adolescence (follow-up). Maturational timing was assessed by self-reports of pubertal status (PDS) in boys and age at menarche (AAM) in girls. Height, weight and waist circumference were measured at baseline and at follow up. Differences in height at follow-up and height gain related to timing of sexual maturation and level of central adiposity (i.e. high or low waist circumference) at baseline were estimated using general linear modelling. At follow-up, median height was 180 cm in boys and 167 cm in girls. Early maturing boys and girls with relatively high central adiposity at baseline were on average 5.7 cm (*P*-value <.001) and 3.6 cm (*P*-value <.001) taller than early maturing boys and girls with low central adiposity. Differences in stature related to central adiposity were less pronounced for intermediate and late maturing boys and girls. Height was lowest in boys (176.6 cm) and girls (163.8 cm) who had matured early and had low central adiposity at baseline. Height gain during follow-up was independent of level of central adiposity, but closely related to the timing of sexual maturation.

Conclusion The association between early timing of sexual maturation and subsequent height was modified by level of central adiposity in early adolescence. The results suggest that early maturity combined with adiposity yields higher stature than early maturity and leanness.

5.0 General discussion

5.1 Methodological considerations

Pubertal changes typically occur at the same time as changes in other areas and both the magnitude and co-occurrence of biological and psychosocial changes may represent one of the most intricate challenges in adolescent research. In epidemiological studies, the study design and the precision of measurements is an overall goal, i.e. to minimize any systematic or random error[155]. Precision in measurement and estimation correspond to reduction of random errors, while validity of a study corresponds to lack of systematic errors.

5.1.1 Precision, the role of chance

The sample sizes utilised in this thesis were generally large, and the role of chance may therefore be less of a concern. Nonetheless, statistical power may decrease and become insufficient due to selection criterions and distribution of subjects according to key variables, such as confounders or effect modifiers. In Paper I-IV the role of chance was tested and statistical significance quantified by P-values, in addition to more informative confidence intervals. Statistical significance, however, provides no information about whether the exposure under study is itself responsible for the observed effect, and cannot address whether differences are important for the health outcomes under study.

5.1.2 Internal validity

The internal validity is defined as the degree to which the results are representative for the particular cohort being studied[156]. There are three general types of bias that can distort the estimation of an epidemiologic study, i.e. selection bias, information bias or possible confounding factors that we can not control for.

5.1.2.1 Selection bias

Even if cohort studies tend to minimise the potential for selection bias, one particular disadvantage may be the losses to follow-up. If individuals entering or remaining in a study display different associations from those who do not, a biased estimate of association between exposure and outcome is produced. This problem may have occurred, as described in the methods section (flow-chart, page 30), but the high response rate (81%), indicates that the study cohort represents the source population fairly well. Still, students who did not want to participate or were absent may differentiate from students included in the cohort. Significant differences in lifestyle have, for example, been reported between responders and non-responders[145;157]. Since more students attended academic study lines and academic study lines traditionally have recruited students from "well-off" families, and higher socio-economic status (SES) has been shown to benefit health, the prevalence of substance use (Paper I and II) and central adiposity/overweight (Paper III and IV) may differ from the true prevalence in the source population.

More important for the issues addressed in this thesis, however, is whether possible social selection towards higher SES, may have underestimated true differences in health outcomes related to SM timing. Previous studies on girls have suggested that early maturing girls may be less academically oriented and also drop out of school at earlier ages[132]. Thus, early maturing girls in the study population may not be representative for early maturing girls in the source population. By using data of 8th and 9th graders (aged 12-15 years) from the 1995-97 survey that represented 95 percent of all adolescents in Nord-Trøndelag County, we explored whether there was a selection of participants related to pubertal timing (PDS-categories). Results showed that the proportion of girls who were followed varied to some extent between early (60%), on time (63%) and late (66%) maturing girls, and between early (61%), on time (56%) and late maturing boys (57%). However, these differences were not statistically significant, and may be due to random rather than systematic error. Nonetheless, among those who participated we could control for potential confounding by parental level of education, as one aspect of SES, which did

not differ between participants who were classified as early, on time (intermediate) or late, neither at academic nor at vocational study lines. Early, on time and late maturing individuals were also equally represented at both study lines. This is consistent with studies that have reported no direct relation between SES and SM timing[158;159].

5.1.2.2 Information bias

Information bias occurs when measurements or classifications of exposure or health outcomes (or both) are inaccurate (i.e. they do not measure correctly what they are supposed to measure), and may be differential or non differential in nature[160]. Non differential bias (i.e. occurs equally in the groups being compared), generally results in an underestimate of the true strength of the relationship.

Pubertal changes and the timing of puberty

Pubertal status usually refers to the level of pubertal development reached by an individual in terms of physical changes. In large epidemiological studies when physical examinations have not been feasible, parental report or self-report has most often been used[146;147;161-163]. One self-report instrument that has shown good validity without being to intrusive is the Pubertal Developmental Scale (PDS), based on the criteria of Tanner[146;147;164] . In the Young HUNT 1 study (baseline), 92 and 93 percent of boys (N=4506) and girls (N=4437) gave adequate ratings of their physical growth and maturation, but the proportion of missing PDS data, was higher among the youngest boys and girls, suggesting that the PDS instrument may be more unreliable in younger ages. We have no indication of differential misclassification related to SM timing, e.g. girls with early or late age at menarche were as likely as others to give adequate ratings of their pubertal status and thus, we do not consider the distribution of missing data to bias our estimates.

Although validation studies have generally shown good agreement between self-evaluations and examinations performed by physicians[146;147;161;165;166], participants may overestimate their current level of physical maturation[165;167]. It is, however, unclear whether early or late late maturing individuals are more apt to under- or overestimate their pubertal changes compared to those who mature on time or intermediate. In this material reliability tests showed good internal consistency between the reported characteristics of sexual maturation in both boys (α =0.85) and girls (α =0.75) and in all timing categories. Thus, boys and girls who for example perceived themselves as relatively late matured were as consistent as others in reporting pubertal changes. It was also overall good consistency between self-reports of pubertal status, and clinically obtained anthropometry data (i.e. height and weight), which also may strengthen our confidence to the ratings that were given.

Age at menarche has been extensively used in epidemiological studies and reliability of self-reported AAM is well established[146;168;169]. An advantage of the Young HUNT study was that girls were asked to report their age at menarche in both years and months, which usually provides more detailed information, making it possible to disentangle those who are early from those intermediate more appropriately. Girls who start to menstruate between 12 and 13 years are at particular risk for misclassification in studies that ask for whole years. For a majority of the participants in our studies (Paper III and IV), self-reports were given relatively short after menarche and possible recall bias should therefore be minimised. Among girls who had not yet started to menstruate or had missing data at baseline, the time interval between AAM and participation was at maximum 4 years. The correlation coefficient (α=.64) between age at menarche reported at baseline and follow-up, among 1232 girls that participated twice was as reported in previous studies[168-171]. Interestingly, the precision of AAM has shown to be nonlinear, i.e. less error has been observed among the earlier and later matured girls compared to those between[169]. AAM is extensively used and may represent the most convenient pubertal marker in studies of girls, but due to wide variation in the sequence of pubertal changes[14;48;172],

and the possible independence of some of the changes, age at menarche may not precisely indicate one person's actual age at pubertal onset.

On the basis of the deviance hypothesis, it has been suggested that most adolescents prefer to perceive themselves as on time or average rather than early or late[2], but in our study more than one third of the participants perceived themselves as relatively early, whereas less than one fifth defined themselves as relatively late. An identical non-symmetrical distribution of early and late maturation was reported in a previous national representative study of Norwegian adolescents (aged 14-16 years), based on a similar questionnaire[149]. Considering that individuals' retrospective perceptions tend to become biologically more accurate during late adolescence as proposed by Dubas *et al.*[137], we would have expected perceptions to be more "normally distributed" among older adolescents in our study population. Being early, however, seemed to be more appraised than being late at all ages, from 13-19 years, with similar patterns for both genders.

To construct measures of SM timing in observational studies, most studies have utilised different trichotomisation procedures, i.e. age and gender specific quintiles, quartiles or, for example, by the use of standard deviations (SD). In some studies the timing measure has only been dichotomous, separating the early maturing individuals from others, or also used as a continuous variable[135]. It is also unclear whether classifications made on skeletal age or APHV are transferable to classifications based on secondary sexual characteristics. Others are based on single item questions, e.g. breast development stage in girls, or stage of voice change in boys to indicate the pubertal stage, but indexes that incorporate several changes in secondary sexual characteristics have been recommended[173]. In this thesis we used age and gender specific quintiles of pubertal status (PDS) and AAM to separate early and late matured individuals from those who were on time or intermediate. This categorisation procedure is used in previous studies, but the literature reveals great variety in methods both between

and within different scientific disciplines, and this may reduce comparability as well as consistency in findings between studies. In a separate analysis of girls' alcohol and tobacco use based on AAM (Paper I), drinking and smoking patterns associated with SM timing in terms of AAM did not correspond with those of pubertal status (Table 1).

Table 1. Frequency of advanced drinking and daily smoking in girls in late adolescence (%), related to SM timing indicated by pubertal status (PDS) and AAM.

		PDS	AAM
Advanced drinking (%)	early	29	21
	on time	20	25
	late	27	17
Daily smoking (%)	early	29	22
	on time	22	25
	late	21	15

Since experimenting with alcohol and tobacco typically occurs in a social context, physical signs of maturation like breast development and somatic growth may be of greater importance for the initiation and advancement in risk behaviours than AAM[122]. According to our data, girls classified as "early" (high PDS score), were more physically matured than girls with early AAM (<12.5 years). Conversely, girls classified as "late" (low PDS score) were less physically matured than girls with late AAM (>14 years) (Paper I). Generally, there is no *one* right answer of how puberty should be measured[174], but this inconsistency related to the pubertal markers suggests that in the planning of future research, several issues related to measures and classification procedures need to be considered. Each marker of puberty may be appropriate depending on which question to be addressed, but our finding confirm that reliance on any one indicator alone may ignore the complexity of pubertal processes and their associations with behavioural outcomes[148].

Central adiposity, overweight and growth

Most previous studies have used body-mass index (BMI) as indirect measure of adiposity, but since the index cannot distinguish between muscular and adipose tissue, there are limitations associated with the use of BMI[175;176]. Studies of children and adolescents have shown a general increase in fat-free body mass with age and with increasing level of sexual maturation[175]. Accordingly, within individuals with equivalent BMI, early maturing boys and girls may have a lower percentage of body fat than individuals who are less sexually matured, and BMI cut offs may overestimate overweight in early maturers and underestimate overweight in those who mature late[177-179].

In Paper III and IV we attempted to address this problem by using waist circumference, which is considered a more reliable indicator of level of subcutaneous fat or central fat deposition than the BMI[177;180;181]. Validation studies (3-19 year olds) have shown very high correlations between waist circumference and trunk fat measured by DEXA scan (0.83 for girls and 0.84 for boys), both related to subcutaneous abdominal adipose tissue (r=0.93) and intra-abdominal adipose tissue (r=0.84)[182] and also less correlated to the timing of sexual maturation than BMI[180;183]. This measure has therefore been recommended as an indirect measure of central adiposity in studies of children and adolescents[68]. In our study, mean waist circumference did not differ significantly between early and intermediate matured girls at baseline, but was slightly lower among late maturing girls. Early maturing boys, however, were less likely to be classified as with “low waist” and central adiposity may therefore be overestimated in this group. The dichotomisation of waist circumference, using the median as cut off, is of course crude and may disguise substantial information about the true relationship between SM timing, adiposity and pubertal growth.

In Paper III overweight was classified according to the International Obesity Task Force (IOTF), that developed BMI cut-off points for children and adolescents that correspond to the widely used adult BMI

cut-offs for overweight and obesity[150]. Despite the reported good overall agreement between IOTF reference standards and others, comparisons have shown noticeable differences for certain ages[150;184]. Discrepancies between early and late adolescent definitions may for example limit the ability to investigate change, but discrepancies may also limit the possibility to generate comparable prevalence estimates[185]. However, other BMI references share the same limitations and yet no single method is considered more valid than others[184].

There are also some limitations associated with height measurements and that not all students had reached their final height at follow-up, especially among intermediate and late maturing boys. Since height velocity is usually very low at the age when follow-up took place[36;43], however, it is considered unlikely that further growth would offset our findings (Paper IV).

Alcohol and tobacco use.

Although adolescents' self-reports of alcohol drinking and cigarette smoking have generally been accepted as reliable indicators of use, young people may overestimate their use[186]. Non-differential overestimation among early, on time and late maturing individuals is not considered to distort our estimates, but late maturing boys and girls may, in an attempt to appear as grown up as possible, be more likely than others to overestimate their use of substances, especially at younger ages. To our knowledge there is no empirical evidence for that, but potential differential misclassification is generally suggested to underestimate true differences in drinking and smoking.

Another source of possible misclassification is the definition of more risky drinking, which is termed "advanced drinking" in this thesis (Paper I and II). Although alcohol drinking is considered risk behaviour, the threshold for misuse, deviancy or delinquency has not been clear. Thus, the individual health risk associated with advanced drinking is largely unknown, and participants may have been

misclassified as advanced drinkers without being it, or vice versa. This is, however, a common feature in most studies of alcohol use and misuse. According to the literature there is no goldstandard in definitions, and in many studies, the use of alcohol is poorly described.

In our definitions of advanced drinking, we assumed that adolescents who consistently reported high "levels" of use (i.e. frequency of drinking and drunkenness in addition to alcohol consumption) also were more likely to be advanced in their drinking practices. This definition embraces that experimentation with alcohol and health-risk behaviour is typical of adolescence and those behaviours, which are considered rare and risky by age 12, are common by age 18. Thus, an increased engagement in these behaviours with increasing age should be expected. On the other hand, by including more items in definitions of risk levels, more sources of random and systematic error may have been included.

5.1.2.3 Confounding

Confounding occurs when the effect of a risk factor on health outcome is explained by an extraneous factor rather than the risk factor under study. A confounder must constitute a risk factor for the outcome, be associated with the exposure variable in the source population from which the subjects arise, but should not be affected by exposure or outcome (although it may affect exposure). For example, pubertal status was considered a confounder for the relation between perceived pubertal timing (exposure) and the use of alcohol and tobacco (Paper II). Pubertal status may explain differences in drinking and smoking between exposed and non-exposed (on time) individuals, and is simultaneously associated with perceptions of being early, on time or late. In cohort studies the confounder must be present among subjects at the start at follow-up. Although confounding is controlled by study design, stratification and by multivariate analysis, other potential confounding factors could have carried additional weight in explanations of findings. Since it is also difficult to isolate the specific factors responsible for the observed relations between exposure (SM timing) and health outcomes, relations may only be indirect and not causal.

5.1.2.4 Study design - shortcomings.

One particular problem associated with adolescents as research objects, may be the tremendous changes that occur over the second decade of life. The transition from early to late adolescence may have affected several behaviours and outcomes in multiple directions, which we were unable to account for. *A time dependent covariate* (i.e. physical growth, diet, exercise, school surroundings etc.) may both affect and be affected by the study exposure (SM timing and level of central adiposity) and thus act as both a confounder and an intermediate variable. The increased drinking and smoking prevalence among early maturing girls, for example, has in many studies been explained by the tendency of these girls to associate with older friends. This peer network may both influence the girls' perceptions of being early (confounding effect), and simultaneously provide a context for health damaging behaviours (intermediating effect).

Similarly, *a recurrent outcome* may both affect and be affected by *a time dependent exposure*, and thus act as a confounder as well as an outcome. For example, increasing BMI levels (recurrent outcome) may affect the timing and tempo of pubertal changes, but these pubertal changes may also affect the likelihood of developing overweight (outcome in Paper III). Although repeated measures may have enhanced the study design, few methods are yet available that properly adjust for confounding by time dependent intermediate or outcome variables.

Changes in growth, maturation and body composition are developmental processes that may differ in intensity and duration within and between individuals, and the timing of each pubertal event may not occur in parallel[48]. Since the time dependent exposure variables, pubertal status and waist circumference were obtained at one single time point and potential change in exposure level, was not taken into consideration, there is some uncertainty associated with these variables. It has, however, been reported a strong tracking of waist circumference from age 11[187]. Few investigators have

evaluated the possible influence of time dependent variation in pubertal status on health outcomes, but Dick *et al* found that adolescents with inconsistent ratings in tempo of development (PDS score) between age 12 and 14, displayed less predictable patterns of substance use than those who were consistent in their ratings[148]. Inconsistency may be a result of misclassification (information bias), but may also, especially in early adolescence, reflect normal time dependent variation in pubertal status and anthropometry, and therefore be substantial.

Studies of growth and maturation based on pubertal status assessments should not be conducted too early or too late in adolescence. Reliable timing classifications demand that a majority of the adolescents have started their pubertal changes, but not yet completed their maturation. The Young HUNT data provided large variability in pubertal status (PDS), especially among boys, which enabled us to reliably separate early and late matured individuals from those who were on time or intermediate matured. Access to pre-pubertal anthropometry data may have warranted us to retrospectively examine the interrelation between early SM timing and childhood over nutrition and to study the full range of pubertal growth(in Paper III and IV). On the other hand, in order to identify for example age at take off for pubertal growth spurt, frequent examinations over a long time period would have been needed, and is usually beyond the scope of a large population based study.

5.1.3. External validity

External validity is about whether the results are applicable to other populations or not, but the term is according to Rothman *et al*. a misnomer, because scientific generalisation, is not simply a matter of statistical generalisation[156]. Ultimately, the goal of a purely scientific study is to contribute to scientific knowledge. The process of synthesising knowledge from observations, involves moving from the particulars of a set of observations to the abstraction of a scientific hypothesis or theory that is more or less divorced from time and place. Scientific generalisations should therefore be interpreted as abstractions. Since populations are considerably more diverse in sociological than in biological phenomena, however, generalisation is more difficult in the social sciences.

Universal statements from this research work may be:

- Early (or rapid) maturation in girls constitutes a risk factor for advanced alcohol drinking and cigarette smoking not only in early adolescence, but also in late adolescence.
- Perceptions of being earlier matured than same aged peers may increase the risk of alcohol drinking and cigarette smoking, especially in combination with high pubertal status.
- The combination of early age at menarche and central adiposity increases girls' likelihood of being overweight during adolescence.
- The combination of early sexual maturation and leanness yields short adult stature.

5.2 Main findings and implications

In the following, the main findings of Paper I-IV and their possible implications will be discussed.

5.2.1 Alcohol drinking and cigarette smoking in adolescence

Our results (Paper I and II) suggest that early maturing girls were more apt to engage in potential health damaging behaviours throughout adolescence. Thus, they were more likely to start drinking and/or smoking at an early age, and they were more likely to get drunk than same aged peers. The persistence of these behaviours from early to late adolescence (Paper I) showed that early maturing girls did not mature out of a potential unhealthy life style and they may be more exposed to more life time health risks than other girls. This is in contrast to previous studies that have reported a more pronounced "catch- up" effect in drinking and smoking between early, on time and late maturing girls[122;129;132]. The long term health consequences of early SM timing appear to be more worrisome for girls than for boys.

Although it is hypothesised that (subjective) perceptions of own timing may be more important for how adolescents act, than their (objective) biological timing[21], the relation between perceived pubertal timing and alcohol and tobacco use has not been extensively studied. One reason may be that perceptions may change from one year to another or from one social context to another[137]. The results presented in Paper II, may indicate that perceptions of being early or late, may be more problematic than perceptions of being mainstream. Perceptions of being "off time" may be more problematic in certain subgroups of young people who are more susceptible to risk exposure. Still, the overall results do not provide much support for the deviance hypothesis.

5.2.1.3 Implications, prevention and future research

Although some risk taking is necessary in the normal developmental process, the results of risk taking may become disastrous[113;114]. Heavy alcohol drinking may reduce the ability of the young people to carry through developmental milestones, such as achieving academic skills and good peer

relationships. Even if it is still unclear whether advanced alcohol drinking is succeeded by later misuse or health problems, for cigarette smoking this is certainly the case. Those who start early also tend to smoke heavily as adults, and they are at the least likely to stop[118]. Young smokers report worse immediate health, both physically and mentally[119]. Tobacco use is not illegal and not directly linked to criminal behaviour; neither does it cause intoxication or obvious acute harm. Youth smoking therefore generates less public anxiety and clinical interest than alcohol and other substance use. Preventive efforts should acknowledge that early maturing girls may constitute a particular risk-group for both alcohol drinking and cigarette smoking.

Because some risk factors for substance use are resistant to change, strategies could seek to address risk by enhancing protective factors[12;188-190]. Early sexual maturation, especially in girls, may denote increased vulnerability, while protection involves enhancing resilient responses to risk exposure. Parental monitoring and support may have a strong protective effect, more so in girls than in boys [188;190]. For example, the risk posed by older substance-using peers, may be moderated by strong attachment or bond between parent and adolescents[191]. More research, however, is needed to investigate the relationships between risk and protective factors as related to adolescent substance use[189;191].

5.2.2 Overweight and stature related to SM timing and central adiposity (Paper III and IV)

"Girls with early feminizing changes will obtain a shorter and rounder body type. Long-legged girls are usually late bloomers who enter puberty past the average age"

This picture of the early maturing girls has been drawn by several investigators. Although we found that SM timing influenced both boys' and girls' stature and body composition, our findings do not fit with the above description. Instead, her body type appears to be largely heterogeneous, depending on nutritional

status or other factors that influence growth in early life. In short, early maturers with a lean body composition ended up shorter than others, while early maturers with a rounder body type ended up as tall as others, similar for both genders.

In girls, central adiposity (i.e. waist circumference above the median) in combination with early sexual maturation nearly tripled the risk of being overweight in late adolescence. We cannot explain the mechanisms behind this finding, but among these girls, AAM may not only reflect the earlier timing of puberty, but also an increased tempo of growth and maturation, which itself may lead to differences in BMI and overweight. Previous studies have shown the rate and progression of maturation (i.e. rapid versus slow) to be more strongly associated with adiposity than the actual timing (i.e. early versus late)[26;102;172;192;193].

Although there was a general tendency for adolescents with high waist at baseline to be taller and fatter at follow-up, the observed heterogeneity in effect associated with central adiposity was more pronounced among early maturers than among intermediate and late matured boys and girls. This joint effect has to our knowledge not previously been described[31;96;97].

Since girls complete their pubertal growth spurt about two years before boys[15;16] and the typical adult fat distribution is gained at an earlier age[194], our results reflect different growth phases for boys and girls and direct comparisons between genders may not be appropriate. Nonetheless, the results suggest that linear growth patterns related to early maturation and level of central adiposity were quite similar for boys and girls (Paper IV). In both genders, height was modified by individual level of central adiposity, and in both genders, differences were more pronounced in early maturers than in those who matured intermediate or late. Our study of overweight, however, revealed quite different results for boys and girls, especially in relation to central adiposity, suggesting that the development of overweight

associated with tempo of growth and maturation may be very different for boys and girls. The gender dimorphism observed in these young participants may involve both genetic and endocrine factors[14]. Differences in leptin secretion is suggested to be central[195;196]. For example, female adipose tissue may be more sensitive to hormones that stimulate leptin production[197]. Others have also reported gender differences in the relation between SM timing and overweight[97;103]. It is important to notice, however, that the overall prevalence of overweight was similar for boys (20%) and girls (19%)(Paper III).

We were not able to study whether students loosed weight or changed overweight status during follow-up, but clearly our data verify the tendency of overweight to track from adolescence into young adulthood. About 70-80 percent of adolescents that were overweight at baseline were also overweight at follow-up. Our data (Paper III) showed that although overweight became more common during four years of follow-up, the major part of adolescent adiposity was already established at the entry of the study in all timing groups (Appendix III). This may be in accordance with research that has suggested childhood to be more critical than adolescence for the development of overweight[187].

5.2.2.4 Implications, prevention and future research

Since body composition may act as a marker for endocrine and metabolic changes in puberty, the body composition may hold key information regarding current and future health[29]. Possible health risks associated with early sexual maturation therefore, may differ between those with a lean body composition and short stature and those with a rounder body type and normal (average) height, especially in girls. For example, a previous Norwegian study showed that early maturing girls who also were overweight had higher risk for developing negative self-evaluations than others[20]. Due to the idealisation of thinness in Western countries, one should expect weight concerns to increase, but results have been inconsistent. A nationally representative study from Finland showed that between 1979 and 1999, as the whole adolescent population gained weight, the reference for self-evaluation changed and

contemporary adolescents were less concerned of being overweight than before[198]. In accordance, an American study showed that although obesity was associated with poor physical quality of life, adolescents with above normal body mass did not report poorer emotional or social functioning than others[199]. Possibly, overweight may affect physical appearance and popularity more than global self-esteem[200]. However, obese children often become targets of early and systematic discrimination with adverse health outcomes. A longitudinal study reported more sadness, loneliness and nervousness among obese (above the 95th percentile) children and adolescents than among others[77].This study showed that obese adolescents were also more likely to engage in high-risk behaviours such as alcohol drinking and cigarette smoking[77]. More longitudinal studies, however, are needed to clarify the relation between SM timing, fatness and psychosocial factors.

Although improved nutritional status has historically shown to benefit growth and maturation, early maturation associated with childhood over nutrition may be adversely linked to adult overweight and obesity as well as chronic diseases[31;70;73-76;92]. The exact prevalence of co-morbidities, however, is to our knowledge not known and no information is yet available on the importance of the degree and duration of obesity. The increase in overweight prevalence though, reflects a population shift toward positive energy balance[68]. Dietary intake and physical activity represent the behavioural and therefore modifiable factors of these balance equations. Prevention of overweight is probably the only feasible option. Policies and actions are needed at a variety of levels, some locally and individually based, some nationally and internationally based[68]. More studies are needed to examine whether or not the current epidemic in childhood over nutrition and obesity will continue to fuel the population trends towards earlier pubertal onset and progression.

Earlier puberty subsequent upon childhood growth may also have implications for future breast cancer risk[201-204]. Although the mechanisms underlying this association are complex, several interacting sex

and growth hormones, that regulate puberty and pubertal growth spurt may be important in the aetiology of breast cancer[204].

Evolutionary theory suggests that in the past few decades, as puberty has advanced, biological maturation has come to precede psychosocial maturation significantly for the first time in our history and care has to be taken not to medicalise contemporary early puberty[94]. The question of age limit for sexual precocity seems not to have any definitive and unequivocal answer and may vary according to the child's population, socioeconomic, geographic and genetic background[14;205;206]. Our social structures, however, have been developed in the expectation of longer childhood, prolonged education and training, and later reproductive competence. This mismatch may create pressures on contemporary adolescents and how they live in society[94]. To truly understand the mechanisms of puberty and also possible changes in onset, progression, and completion, we need longitudinal data from diverse samples of children[174;207]. A broad framework and integration of longitudinal and experimental research will also provide a more complete and rich understanding of puberty as a possible early marker of interactions between environmental conditions and genetic susceptibility[14].

6.0 Conclusions

- For girls, but not for boys, early SM timing was associated with more advanced drinking and higher frequency of smoking in late adolescence. In boys, late SM timing was associated with reduced risk of advanced drinking.
- In both genders, perceptions of being earlier matured than same aged peers was associated with more frequent drinking and smoking, especially in combination with high pubertal status.
- In girls, the association between SM timing and overweight was modified by level of central adiposity. The combination of early central adiposity and early age at menarche was associated with overweight in late adolescence.
- In both genders, the association between SM timing and subsequent height was modified by level of central adiposity. Early SM timing combined with early central adiposity yielded higher stature than early SM timing and leanness.
- Differences in height (both genders) and overweight (in girls) at follow-up, related to level of central adiposity at baseline, were more pronounced among those who matured early, compared to those who matured intermediate or late.

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