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COGNITIVE ABILITY, ALCOHOL USE AND ALCOHOL-RELATED HARM

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Cognitive ability has been shown to be inversely associated with several health outcomes, both somatic and psychiatric. The findings regarding the association between cognitive function and alcohol-related outcomes have however not been consistent. Furthermore, there has been a lack of knowledge regarding possible differences between genders and what mechanisms there would be that could explain the association. Also, information regarding school performance and alcohol-related outcomes has been needed. The overarching aim of this thesis was to further investigate the association between cognitive function, alcohol use and alcohol-related harm.

Three different data bases were used in this thesis, The Swedish Conscript Cohort consisting of 49 321 Swedish males, the Evaluation Through Follow-up data base with a total of 21 809 Swedish men and women and School Register data with a total of 213 395 Swedish men and women.

In study I, using the Swedish Conscript cohort, we investigated the association between IQ-test results from late adolescence and alcohol-related hospital admission and death. An inverse, grade association was found for both outcomes. This was a longitudinal, cohort study.

In study II, using the Swedish Conscript cohort, the association between IQ-test results in late adolescence and alcohol consumption, measured both as total alcohol intake and pattern of drinking. Lower IQ-test results were found to be associated with a higher alcohol consumption, regarding both outcomes.

In study III, using the Evaluation Through Follow-up data base, we found an inverse graded association between IQ-test results measured in childhood and alcohol-related hospital admission and death. There seemed to be no interaction for gender in the association, and socio-economic position as adult was assessed to at least partly mediate in the found association, for both outcomes.

In study IV, using School register data, we found a graded, inverse association between grade point average from 9th grade and alcohol-related admission to hospital, for both men and women. IQ-test result did not seem to be a confounder in the association.

In conclusion, we found that IQ-test results and school grades were inversely associated with alcohol use and alcohol-related harm. The results were similar for men and women, where investigated and socio-economic position as adult, was assessed a possible mediator in the association between intelligence and alcohol-related harm.

LIST OF SCIENTIFIC PAPERS

I. Sjölund, S, Allebeck, P., Hemmingsson, T. (2012). Intelligence quotient (IQ) in adolescence and later risk of alcohol-related hospital admissions and deaths—37-year follow-up of Swedish conscripts. Addiction, 107(1):89-97.

II. Sjölund, S., Hemmingsson, T., Allebeck, P. (2015). IQ and level of alcohol consumption - Findings from a national survey of Swedish conscripts. Alcoholism: Clinical and Experimental Research, 39(3):548-55

III. Sjölund, S., Hemmingsson, T., Allebeck, P. (2015). IQ and alcohol-related morbidity and mortality among Swedish men and women – the importance of socio-economic position. Accepted, The Journal of Epidemiology and Community Health

IV. Sjölund, S., Hemmingsson, T., Falkstedt, D., Allebeck, P. School grades and alcohol-related disease. Manuscript

CONTENTS

LIST OF ABBREVIATIONS

EFT/UGU	The data base Evaluation Through Follow-up
HR	Hazard Ratio
ICD	International Classification of Diseases
IQ	Intelligent Quotient
LISA	The Longitudinal Integration Database for Health Insurance and Labour Market Studies
LOUISE	The Longitudinal Database of Education, Income and Employment
OR	Odds Ratio
SEP	Socioeconomic position
Stanine	Standard-Nine

1 BACKGROUND

The use of alcohol is part of the social life in many cultures over the world. It is often associated with pleasure, reward and celebration. However, the consumption of alcohol may also cause harm. Several risk factors for alcohol misuse have been identified, among those, factors that are part of a social context, such as norms, and others that are related to the individual, for example attitudes towards the use of alcohol within a family (1). There is, however, still more to learn about possible risk factors for alcohol misuse. An individual factor that recently has been shown associated with several health outcomes is cognitive ability. The association between cognitive ability, alcohol use and alcohol-related harm, is what this thesis aimed to investigate.

1.1 INTELLIGENCE

1.1.1 The concept of intelligence

The well-known argument for existence, "Cogito, ergo sum" by René Descartes, draws attention to the fundamental meaning of the ability to think. Just as pivotal as cognition is for the recognition of being, just as elusive it seems to define. This is certainly also true for the concept of intelligence. These two terms, "cognition" and "intelligence" are by some used synonymously, and by others, not. In this thesis, the term "intelligence" will be used for what is measured by test of intelligence quotient (IQ). Cognition may be described containing a wider array of abilities than intelligence, including, for example, perception and executive functioning (2) The richness in definitions of intelligence mirrors both the great interest in and lack of sufficient tools for understanding of what we mean, when we say "That was a really clever person". Down below are a few examples of definitions of intelligence (3):

"It seems to us that in intelligence there is a fundamental faculty, the alteration or the lack of which, is of the utmost importance for practical life. This faculty is judgement, otherwise called good sense, practical sense, initiative, the faculty of adapting ones self to circumstances". A. Binet and T. Simon.

"An intelligence is the ability to solve problems, or to create products, that are valued within one or more cultural settings". H. Gardner,

"The capacity to acquire capacity". H. Woodrow

[Intelligence] . . . involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test-taking smarts. Rather it reflects a broader and

deeper capability for comprehending our surroundings—"catching on," "making sense" of things, or "figuring out" what to do. Linda Gottfredson et al

When reading the above definitions, it is easy to grasp the significance of this ability in several aspects of life. In fact, it may be considered one of the most highly valued skills, both within education and society as a whole (4). Intelligence, as measured by IQ, is normally distributed within a population, and has generally been expected to be stable for an individual in a life perspective (5, 6).

Over time, intelligence has been found to increase, generation by generation. This has been labeled the "Flynn effect", named after researcher James Flynn who wrote about the phenomenon in the 1980's, although the empirical evidence can be found described earlier by e.g. Tuddenham (7-9). The cause of this gain in intelligence is not known, but eight different theories have been suggested to explain why. Among these, improved education, test management, nutrition, genetics and changed attitudes regarding the tests, are found (10-12). However, lately there has been indications that the Flynn effect might have come to an end (13). Intelligence, as well as other behavioral aspects, is heritable to a certain degree. The importance of heritability does, however, seem to differ by age (increasing by age) and socioeconomic position (decreased for low SEP) (14-16).

Socioeconomic status when growing up, has an effect on the development of an individual's neural system. Although the largest effects are seen among the lowest levels of socioeconomic position, the effect is present at all levels in varying degree. It has been hypothesized that parent-child interaction, cognitive stimulation and pre-natal factors might be the mechanisms that would explain how socio-economic status and cognitive development are associated (17). Certain factors have been suggested to improve intelligence, both biological (e.g. breastfeeding) and social (communication with children) (15, 18). One factor that does seem to have influence on intelligence is education, and physical exercise has been shown to help maintaining IQ (15).

1.1.2 The construct of intelligence

Intelligence is considered to be an ability, which varies between individuals, but also somewhat within an individual depending on criteria used , domain and occasion (19).

Historically, there have been plenty of models suggested to describe how intelligence is structured, some less influential than others. Conceptually, a main difference among models for intelligence, has been whether they include a general factor of intelligence, 'g', or not. Another, if different domains of intelligence are hierarchal or not. In 1904, Spearman launched a theory called the "Two Factor theory of intelligence", which described his findings of one factor that seemed to be relevant for all intellectual tasks, (g) and another that was specific for each task, (s). Opposing that view, was a multi-factorial model suggested by Thurstone, where 6-7 so called 'Primary Mental Abilites', for example 'Word Fluency', 'Induction' and 'Perceptual Speed', were identified as different domains of intelligence. Rather than presenting IQ as a single measurement, Thurstone was interested in showing an intellectual profile, which in his opinion would give a more accurate and rich description of an individual's mental abilities (20). Another of the more famous models of intelligence, is the one by Cattell and Horn. In this model, they suggest five general factors, of which two, 'fluid intelligence' (Gf) and 'crystallized intelligence' (Gc) are often found in the literature. The fluid intelligence is what is used when facing new tasks, more influenced by biology than the crystallized, which is more the result of learned experience and most notable in verbal and conceptual tasks (21). Today, there is consensus within theory of intelligence, that there is a general factor, 'g', as suggested by Spearman, for which about 50% of the variance among different mental tests in a large population is accountable (22).

1.1.3 The testing of intelligence

Measuring of intelligence is part of the field of psychometrics, that is, testing intended to yield objective measurements of an individual's psychological characteristics. Other than testing for intelligence using IQ-tests, personality traits, attitudes and knowledge are, for example, subjects for such testing. The critique for the testing of intelligence has mainly been concerned with the possible over-simplification of a complex ability, not measuring what it is intended to measure, and the risk of misuse of the tests (15). However, the general understanding is that it is possible to measure intelligence, and that intelligence tests are among the most accurate psychological assessments available (5). The branch of psychology which is interested in individual differences is called differential psychology, which is opposed to the other branch, called experimental psychology (23).

An early version of intelligence testing, was performed in ancient China. An exam, "keju", was given to candidates of civil service in the 7th century AD, where the ability to memorize and interpret works of Confusion was assessed (24). In modern time, the test developed by Binet and Simon in 1905, has had great impact in the area of intelligence measurement. Today, the factor analysis, first suggested by Spearman, is widely used. Common types of items in an intelligence test are 'analogy', 'odd-man-out' and 'sequences'(25).

1.1.4 Controversies regarding intelligence

Research within the field of intelligence, devoted to investigating differences between groups - mainly between genders and ethnic groups - have raised debate. Concerns have been expressed regarding how intelligence, gender and the ethnic groups have been defined, ultimately dependent on the social, political and cultural climate, resulting in skepticism regarding the interpretation and purpose of the research (5, 26-29).

The field of public health has, traditionally, been focused on finding structural explanations for social inequalities in health. Environmental factors and the social structure of society, including working life, have been the main areas which have been investigated as possible and, potentially, amenable causes of these inequalities. Intelligence is an individual characteristic, which together with personality, have emerged as alternative explanations for social inequalities in health (30, 31). Studies investigating social inequalities in health often use education, income or occupation as a proxy for an individual's socio-economic position. These three proxies are inter-related, but measures different aspects of the concept of socio-economic position (32).

However, the meaning of socio-economic position has been debated, whether it is merely a surrogate for intelligence, or alternatively, a mediator due to the close association between e.g. intelligence and educational level (33), rather than socio-economic position in itself being the generic explanation for the socio-economic differences in health (34-40). The controversy arises when lifting your eye from the neat, although complex, figure of the Directed Acyclic Graph illustrating the different possible pathways, and try to understand the ethical and moral implications of the suggested pathways. Health differences in a population may be described as being 'fair' or 'unfair', where, for example, they could be considered fair, if they are the result of a behavior with negative consequences for health which the individual has made a free choice to exert, and unfair, if it is less of a choice (41). Letting the

question about free choice alone, the policy implications will be quite different, depending on what is considered fair and unfair to the public.

1.2 INTELLIGENCE AND HEALTH

Intelligence has been shown to be associated to several health outcomes. The research field aiming at investigating the association between intelligence and health has been named "cognitive epidemiology" (42). Already in 1925, Terman, searched an association between intelligence and health in his "Genetic studies of genius" (43), and then, in 1997, a call was made for including intelligence and epidemiological studies (44). Today, the association has been found among both psychiatric (45, 46) and somatic diagnoses (47, 48), and is well established for all-cause mortality (49-56). Typically, the association is inverse, that is, a higher intelligence is associated with a lower risk for ill-health or death. This type of association is however not omnipresent, there have been studies where no, or a positive, association have been found, (46, 50, 57, 58).

Four mechanisms have been brought forth to explain as to how and why IQ would be associated with longevity (59):

1) Intelligence may be a feature which is in accordance with a systemic bodily efficiency – that is, a well-functioning intellect occurs in a well-functioning body

2) Early life conditions, biological or environmental, may be the common cause to both level of intelligence and health

3) Intelligence means capability to make choices in life which furthers health

4) Intelligence is associated with education, which places the individual in a certain socio-economic position with bearing on health

The first suggested mechanism is formulated within the 'System Integrity Hypotheses' and suggests that it should be possible to sift out a marker of system integrity, which both is associated with intelligence and health, and theoretically plausible. Several markers have been proposed, e.g. reaction time, physical co-ordination and bodily asymmetry. The explanation of a body with a system integrity, to the association between intelligence and health, has not yet been confirmed, though (58, 60).

Support for the second suggested mechanism, has also been scarce so far, although examined more in the literature than the first described mechanism. The possible influence of, for

example, socioeconomic circumstances as a child on the association between intelligence and health has been shown to be rather low (61) (54).

Regarding the third mechanism, there are examples found that individuals with a higher IQ tend to make certain decisions regarding their lifestyles with an impact on health, such as diet, e.g. vegetarianism and physical activity (62, 63). For smoking and the association with IQ, there have been some contradictory results, regarding prevalence of smoking, level of smoking and quitting of smoking (64-67). It is, however, very likely that intelligence is involved in all three stages of health promotion and prevention (primary, secondary and tertiary prevention), given the importance on how well you manage new situations and information that will have an impact on health (68).

Finally, socioeconomic position as adult has been suggested to mediate the association between intelligence and later health. As described above, the close association between intelligence and education might lead to the conclusion that socioeconomic position is rather a proxy for intelligence, than a variable of its own right. Support for this suggested mechanism has been found in studies investigating the association between intelligence and mortality (58, 69-72).

1.3 SCHOOL GRADES

School grades are markers of school performance. Both school grades and intelligence predict academic achievement, and have been shown to correlate with about 0,50 (19). However, intelligence tests and school grades should not simply be regarded as proxies for each other. In a Swedish context, they differ regarding at least three perspectives: 1) To achieve high grades, perseverance is needed to a larger extent, than to perform on a cognitive test, 2) School grades is a an established, and socially recognized marker of performance while cognitive testing is less used and 3) School grades is used to apply to higher level of education (73). The association between intelligence and academic achievement may be seen to have an interaction, where intelligence is a resource in acquiring knowledge, and knowledge enhances the ability to learn (intelligence) (74). However, there are several other factors than intelligence that have been shown to influence school grades, such as motivation, family background and personality (73, 75).

1.4 ALCOHOL CONSUMPTION AND PUBLIC HEALTH

Alcohol is a since-long, known concern within the field of public health. The harmful consumption of alcohol is listed by the WHO as one of the top five risk factors for disease, disability and death, globally (76). Within the project Global Burden of Disease (GBD), alcohol consumption has been assessed to contribute to about 4% of the total mortality and 4-5% of the disability-adjusted life-years. The burden of disease due to alcohol consumption is

greater among low-income countries than among high-income countries and greater among the poor than among the well-off within countries (77).

In the EU, the 1-year prevalence of alcohol dependence was in 2010 estimated to 3,4% (78). Alcohol use disorders (dependence and abuse) has a prevalence of 3,6% globally, which is one of the highest prevalences among the mental disorders in the world (77). It is has been shown that individuals in general with an alcohol use disorder have an increased mortality for conditions such as liver cirrhosis, mental disorders, death by injury in comparison with the general population (79).

1.4.1 Alcohol consumption

1.4.1.1 Pharmacokinetics

The main players in the metabolism of alcohol are the two enzymes alcohol dehydrogenase and aldehyde dehydrogenase. Firstly, ethanol is oxidized into the metabolite acetaldehyde, which later is further oxidized into acetate and water. These two enzymes are polymorph, and have been suggested to influence the risk of harmful consumption of an individual. The activity and functionalism of the enzymes polymorphisms have been shown to vary with ethnic origin, gender and age (1).

1.4.1.2 Diagnoses related to alcohol

There are medical diagnoses which are the result of alcohol consumption only, and others where alcohol consumption just is a component cause (80). The size of the effects is dependent on dose and duration of consumption in a linear manner (81), although J-shaped associations, have been found for coronary heart disease and diabetes mellitus. These findings have, however, been highly debated and recently also contradicted (82).

Alcohol affects health in mainly three ways: Firstly, there are the direct effects of ethanol, which are either toxic or, which also has been reported, beneficial. Then, there are the secondary effects due to the effects of alcohol on the central nervous system causing alcohol intoxication, such as accidents and injuries. Thirdly, the use of alcohol may by itself be a disorder, amplifying the toxic and intoxicating effects of ethanol (83).

Alcohol has been considered a necessary cause for more than 30 diagnoses in the ICD-10, and a component cause for more than 200 diagnoses. Of these, cancer, cardiovascular

disease, alcohol-use disorders, alcoholic cirrhosis of the liver and injuries are the largest diagnostic groups (77).

Cancer due to consumption of ethanol is believed to be caused by its metabolite acetaldehyde (84). Cancers of the mouth, pharynx, larynx and the oesophagus have been shown to be most strongly associated with level of alcohol consumption (85). Liver cirrhosis is the last stage of alcoholic fibrosis, which is the normal response for the liver to react to an injury (86).

The consumption of alcohol has been shown to have negative effects for some cardiovascular disorders when heavy drinking is present (e.g. hypertension, supraventricular arrhythmias and cardiomyopathy), but also some positive, such as less risk of ischemic stroke and atherothrombotic conditions, for light-to-moderate drinking of alcohol (87).

Alcohol use disorder is the term introduced by DSM-5, which was previously described in two separate diagnoses, abuse and dependence in DSM-IV (88). The process from merely consuming alcohol to become dependent, or addicted, has been shown to biologically involve the dopaminergic systems, as well as several other systems of hormones and neurotransmission. Addiction is regarded to be a chronic condition, where a tolerance of alcohol and symptoms of withdrawal may develop (89, 90). Alcohol use disorder share features with several other neuropsychiatric disorders, why it is likely that it, as the others, has a multifactorial background (91). Genes and environment are involved to an approximately equal extent, with an heritability of about 50% (92).

1.4.2 The epidemiology of alcohol

The consumption of alcohol in a population is dependent on several factors. Individual features, such as gender, genetics, socio-economic position and age as well as, societal, such as culture, access and price of alcohol, all influence level of alcohol consumption (93). Furthermore, the relation between how much a person drinks and the consequences thereof is not straightforward. Gender, age and socio-economic status have been suggested to moderate the effects of alcohol on risk of experiencing adverse events due to consumption (94).

Much is written about differences in level of alcohol consumption between genders. Women across cultures drink less and, as a consequence, it has been said, suffer less harm of drinking alcohol, than men (95, 96). It has even been stated that the difference in alcohol consumption between men and women is “one of few universal gender differences in human social behavior”(97). Recently, however, studies have suggested that levels of consumption have started to converge for the genders, which might be due to societal changes and norms (96, 98, 99).

Several explanations, genetic, and societal, have been suggested as to why women use less alcohol than men. But, studies on gender, genetics and risk of alcoholism have shown divergent results, leaving the matter of the relevance of genetics unsolved (100) . The female role in society, has been perceived as being less tolerant for high consumption of alcohol, where expectancies of moral responsibility, control of sexuality and a maintaining of traditional gender roles have been important factors contributing to different use of alcohol between women and men (95, 97).

There are reasons to believe that the consequences of alcohol use differ between women and men. For example, even though women are less likely to drink, they have been suggested to suffer more adverse effects (101). For example, it has been shown that women reach higher levels of ethanol in the blood, than men, after consumption of the same amount of alcohol. Explanations for this finding have proposed to be a smaller body size, less body water content and in older age, a lower activity of the gastric alcohol dehydrogenase, for women, than for men (102). This is also in line with what has been found regarding, for example, a more rapid development of an alcohol use disorder after first exposure, higher risk of developing heart disease as a consequence of alcohol consumption and acquiring brain damage for women, than for men. In all, female alcoholics have, in general, been shown to have greater death rates than their male counterparts (103).

Although shown important for many other health outcomes, socio-economic position as a child has not yet been observed as a strong predictor of risky alcohol consumption as adult (104, 105). However, patterns of alcohol consumption, and consequences thereof, have been identified with regards to socio-economic position as adult. Regarding the consumption of alcohol, it seems that individuals with a high socio-economic position tend more often to be consumers of alcohol, and drink more often, whereas the total alcohol intake is higher among those with low socio-economic position. As for the consequences of alcohol consumption, such as alcohol-related problems, diagnosis and mortality, they have been seen more common among those with low socio-economic position (93, 106-109).

As for age, consumption of alcohol have been shown to increase during adolescence, and then decrease after being at its height in the early twenties (110).

1.4.2.1 Alcohol consumption in Sweden

Historically, during the 18th-19th century, the level of alcohol consumption has been high in Sweden. Efforts to take control of the production and consumption of alcohol were made early on, where an example is the introduction of state monopoly of the vodka production (although for economic reasons) by the king, in 1775 (111). A powerful stakeholder was later on the temperance movement, which had its part in the prohibition of production of spirits in

the home in 1855. The rationing of alcohol which had been introduced during the first World War, was abolished in 1955, leading at first to an immediate increase of consumption of alcohol, which was met with an increase of price. Taxation has since been the major instrument to steer level of alcohol consumption, in Sweden, together with limited access (112).

1.5 INTELLIGENCE AND ALCOHOL-RELATED OUTCOMES

The association between intelligence and alcohol use, measured and alcohol-related harm has been investigated in earlier literature, with inconclusive results.

Regarding intelligence and alcohol consumption measured as alcohol intake, a positive association have been shown between high cognitive ability and a high total alcohol intake for men (113), for women a drop in intake was shown for the highest scoring group in comparison with the next highest scoring group (113). A null association between intelligence and alcohol intake, has also been reported (114).

For pattern of drinking, measured as binge drinking, an inverse association has been shown with IQ (115, 116), as well as no association (117). Frequency of drinking has, on the opposite, been shown to have a positive association with cognitive ability and verbal development (113, 118). These findings are in line with the results studies focusing on drinking problems, reported by the CAGE screen, which have shown a positive association to high cognitive ability (113, 119). The CAGE screen is an instrument consisting of four questions, intended to be useful in the diagnosing of alcoholism. The four questions are if the individual has 1) felt a need to Cut down on drinking, 2) ever felt Annoyed by criticism of drinking, 3) had Guilty feelings about drinking and 4) ever take morning Eye-opener (120). However, a high IQ has been shown to be associated with a lower prevalence of hangovers (121). Alcohol-related diagnoses have been found to be inversely associated with IQ for men (122-124), as well as no association (125). Additionally, alcohol use has been shown to begin at an earlier age for children with a higher IQ test score, than for those with a lower test score (126).

Altogether, the found associations between intelligence and alcohol-related outcomes are difficult to interpret. It could be the differences in the outcomes themselves which causes discrepancy in the direction of the associations. This would not be sufficient as explanation though, as it seems that also similar outcomes give different results. Since the consumption of alcohol seems to vary over time and between populations, it is reasonable to assume that the association between intelligence and alcohol-related outcomes may vary similarly.

In fig. 1, the possible mechanisms explaining the association between intelligence and alcohol-related outcomes are depicted. It has been shown that socio-economic position as adult at least partly could be mediator between intelligence in the study investigating alcohol

induced hangovers, and that childhood circumstances probably did not confound the association (121).

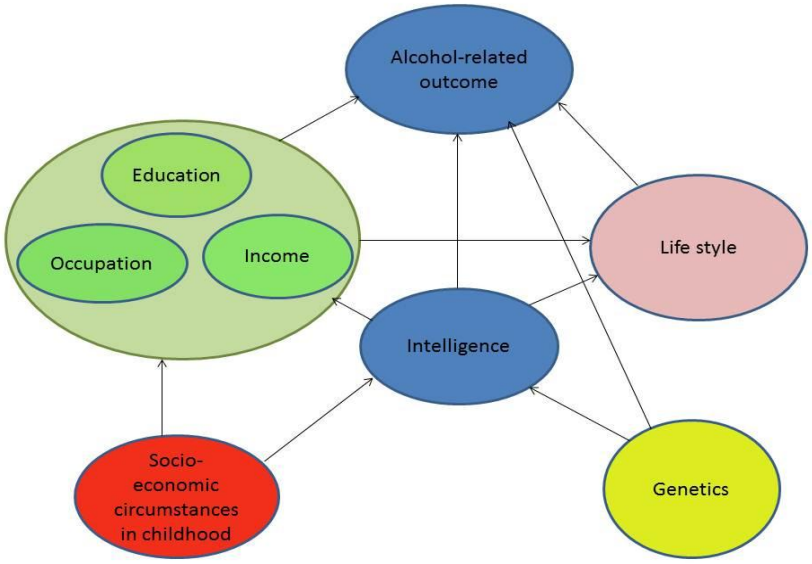

Fig.1 Possible pathways explaining the association between intelligence and alcohol-related outcomes

1.6 SCHOOL PERFORMANCE AND ALCOHOL-RELATED HARM

Education is well-known to have bearing on health. Studies on the association between education and diseases relevant for public health, such as cardiovascular disease and diabetes type 2, have been shown previously (127, 128).

More often, when education is used as a variable within epidemiology, highest level of education or number of years spent in education, are used as marker for education. School grade is a less used index of education, and specifically, little has been studied about school grades and alcohol-related outcomes.

As with intelligence and alcohol-related outcomes, there have been inconsistent results regarding the association between school performance and alcohol-related outcomes. Grade point average has been found to not be associated with alcohol abuse and dependence (129), a high achievement in first-grade math has been shown to be associated with less risk of alcohol abuse and dependence, among boys but not girls (130). Furthermore, high school grades have been found associated with less heavy drinking, but not with frequency of drinking, nor symptoms of alcohol abuse or dependence (131).

Given what has just been described regarding intelligence and alcohol-related outcomes, it would be reasonable to hypothesize that school grades would be associated with alcohol-

related outcomes in a similar way. More than that, school grades could be regarded as a social marker of success, as described recently. The achievement of a certain school grade may be considered a social event, which has been suggested to be associated with life style behavior, such as alcohol consumption (130). Our above suggested hypothesis, that school performance, measured as grade point average, is associated with alcohol-related outcomes has just recently been confirmed in another Swedish study (132).

1.7 KNOWLEDGE GAP

Previous research suggests that the association between, for example, cognitive function and mortality should be found also for alcohol-related outcomes. The picture regarding the association between cognitive function and different alcohol-related outcomes has however shown to be diverse. Little has been known regarding outcomes such as risk of being hospitalized or even die of an alcohol-related diagnosis, in this context. Furthermore, within the field of cognitive epidemiology, there has been a lack of studies investigating possible differences between genders, as many of them have been studies made on a male population. Also, understanding why and how cognitive function is associated with different health outcomes is needed, why possible mechanisms for the association should be investigated.

2 AIMS

The overall aim of this thesis was to investigate if intelligence and school performance are associated with alcohol-related outcomes. We also intended to explore possible mechanisms in any found association between intelligence and alcohol-related outcomes, and if they were similar between the genders.

2.1 SPECIFIC AIMS

The specific aims were to investigate if:

1) - there is an association between intelligence measured in adolescence/childhood and later alcohol-related disease and death.

2) - the association between intelligence measured in childhood and later risk of alcohol-related disease and death differ between the genders.

3) - socio-economic position as adult is a mediator in the association between intelligence measured in childhood and later alcohol-related disease and death.

4) - there is an association between intelligence and alcohol consumption measured in adolescence.

5) - there is an association between school grades and later alcohol-related diagnosis.

A presentation of the general outline of this thesis is found in fig.2.

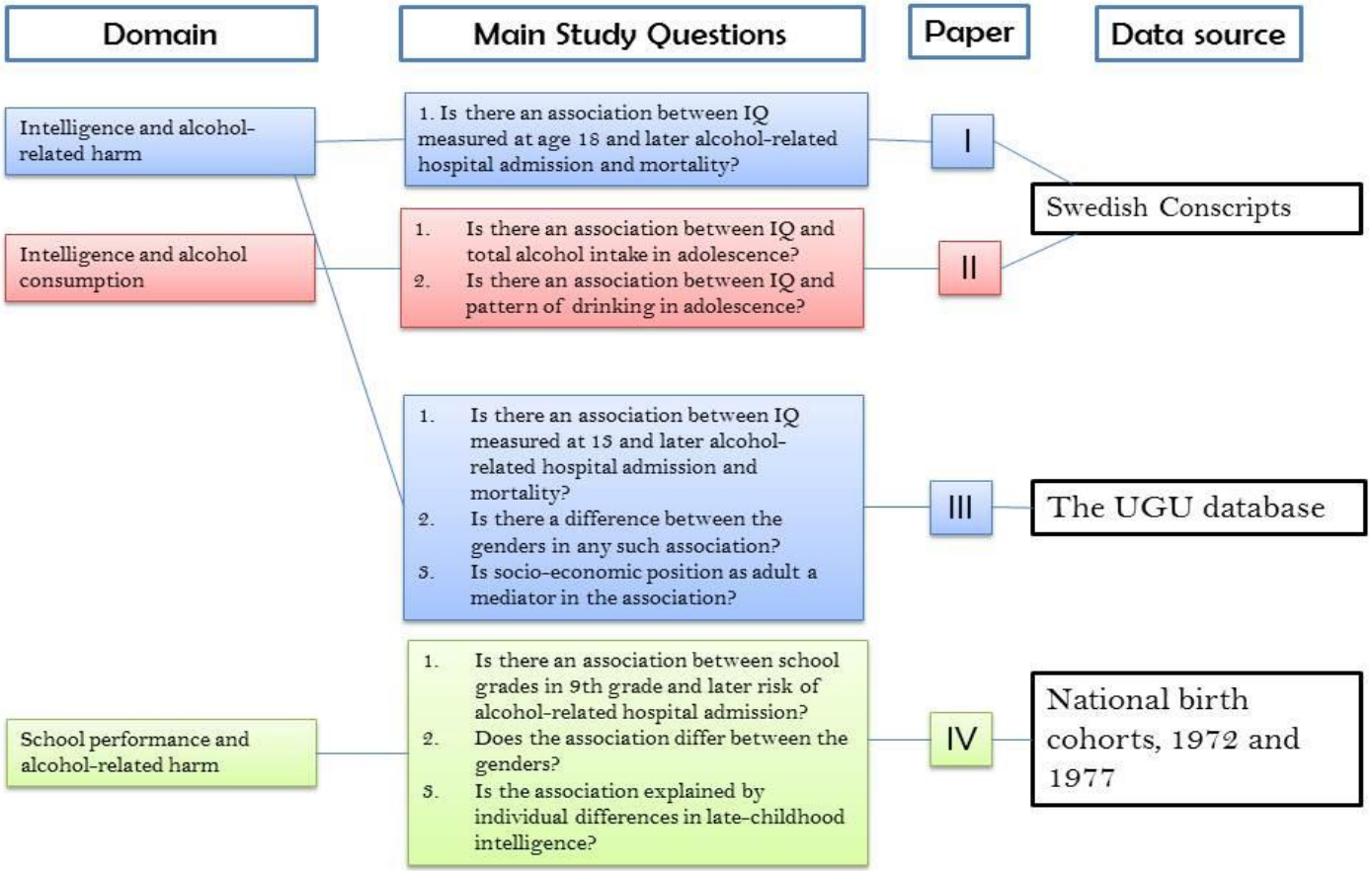

Fig.2 General outline of thesis

3 METHODS

3.1 STUDY POPULATIONS

3.1.1 The Swedish Conscript cohort

In Sweden, military enlistment procedures have been common since long. In 1812, mandatory military service for Swedish men between ages 21-25 years was introduced. By the enforcement of the Army Act 1901, new demands were put on the conscription procedures as a result of administrative changes within the military. According to the law regarding conscription in 1914, every male was expected to take part in the military service the year he turned 20 (133).

From the year 1968, the conscription procedure was made more extensive than before, with two days of examinations aimed at assessing the capacity of the individual for military service and to find an appropriate position within the military (134, 135). From 1996, with the agreement of proposition 1995/96:12, due to a changed political climate, conscription was no longer mandatory for all Swedish males.

In this thesis, the Swedish conscript cohort consists of men conscripted 1969-70, born 1949 (10% of the population), 1950 (22% of the population) and 1951 (67% of the population).

At conscription, two questionnaires were completed. The first had questions mostly regarding social background (upbringing, school adjustments, etc.) and the second concerned use of different substances (e.g. tobacco, alcohol, narcotic drugs). Furthermore, a test called "enrollment-test" (I*nskrivningsprov, I-prov/I-test*), was performed, which was intended to capture the candidates "ability to assimilate military education", that is, a test of intellectual ability (133, 136).

A physical examination was conducted by a physician, and a psychical by a psychologist, who performed a structured interview. If asked upon by the conscript, or indicated by the examinations, a psychiatrist was consulted. The results of the psychologists' interview were checked for reliability, regularly.

In total, the study population consisted of 49 321 Swedish males, which was about 97% of the source population. The 2-3% drop-out was mostly due to severe disability or congenital disorders.

3.1.2 The Evaluation Through Follow-up database

The Evaluation Through Follow-up (ETF/UGU) database was started in 1961 with the aim to evaluate the Swedish school system (137, 138). It currently contains data on samples from eight Swedish birth cohorts born between1948 and 1992. The majority of the sample size is about 9 000 individuals, with the exception of those born 1948 (12 000 individuals) and 1977 (4 500 individuals).

The information collected within the project may be categorized into:

1) Basic data

Ex. school administrative data, education and occupation of parent, IQ-test results, questionnaire responses from pupils, parents and teachers

2) Follow-up data from within the school system

Ex. school administrative data and questionnaire responses from the pupils

3) Follow-up data from outside the school system

Ex. questionnaire responses about adult education, occupation, military classification tests and records on study finance

In this thesis, the samples born 1948 and 1953 were used, with a total of 21 809 men and women.

3.1.3 School register data

In Sweden, Statistics Sweden collects data for the Swedish National Agency for Education regarding pre-school, school and adult education. It is mandatory for schools to give data to Statistics Sweden, every year. Within the registers for schools, information regarding grade point average from both compulsory school and upper secondary school is found. The statistics is routinely evaluated regarding quality, and corrected if found to contain too much error.

3.1.4 Exposures

3.1.4.1 IQ-tests

In this thesis, two different IQ-tests have been used. One for the cohort of Swedish, male conscripts performed at about age 18 (study I and II), and the other from the UGU data base (study III), performed at about age 13.

The two tests are described down below:

<u>IQ-test, Swedish conscripts cohort</u>

The first version of the I-test was used for the first time during conscription 1944. Since then, the test went through several changes, until the version used for the cohort used in this thesis. The test battery administered at conscription 1969-70, consisted of four different parts, where the items were ordered by increasing difficulty along the test. It was also a paper-and-pencil test where optically readable response sheets were used. Prior to each sub-test, instructions were given, and a slight time pressure was applied. This test differs somewhat from non-military ability tests, in that the technical ability has been given a more prominent position.

The four sub-tests were, with description:

1) Instructions: consisted of 40 items. The sub-test was intended to test logical inductive ability, as well as verbal abililty to follow instructions

2) Concept discrimination: consisted of 40 items.The sub-test was aiming at testing both logical inductive and verbal ability, where the respondent should find which word, out of five, that do not belong with the others

3) Paper form board: consisted of 25 items. Spatial ability was tested by requiring of the respondent to chose which of four groups of geometrical figures, make out the figure serving as a model.

4) Technical comprehension: consisted of 52 items.Technical ability was tested through the chosing of the correct alternative out of three, which best described the application of a basic technical or physical property in a drawing.

The test has been shown to have a test-retest reliability of 0,81 with a time interval of 1-3 years. The predictive validity of the test has been shown to be acceptable (133).

IQ-test, UGU

For the cohorts born in 1948 and 1953 in the UGU data base, the test battery was identical at the two testing occasion in 1961 and 1966, when the subjects were 13 years old. The same test has been used also within the Project Metropolitan (Jansson 1975, Dahlbäck 1980). The test battery consisted of three different parts, 40 items each, measuring intelligence according to Thurstone's theory of abilities.

The three parts were, with description:

1) Opposites: finding the opposite of a word, chosing among 4 alternatives

2) Number series: complete a series of numbers, the first six given, with another two numbers

3) Metal folding: finding the correct three-dimensional object, among 4 alternatives, of a flat-piece of metal, with drawn bending marks

The test was a paper-and-pencil test, with answers written down directly in the test, and was performed in a classroom with the classroom teacher administrating the test. Each test part had a time limit; opposite 10 minutes, number series 18 minutes and metal folding 15 minutes.

The reliability of this test have shown to be about 0.9 (139) and a correlation of 0,78 to the Swedish military test (140-142).

3.1.4.2 School grades.

In study IV, grade point average (GPA) from the 9th grade, which is the last year of compulsory school in Sweden, was used as exposure. The average grade was calculated from the assessment of 18 different subjects, where the grading system at the time was from 1 (lowest grade) to 5 (highest grade). As English and mathematics were offered at two different levels, one more advanced than the other, every grade from the more advance course was computed equivalent to one grade higher than in the general course. Where the grade in physical education lowered the grade point average, it was excluded from the computation.

3.1.5 Outcomes

3.1.5.1 Alcohol-related admission and mortality

In study I and III, alcohol-related admission to hospital and alcohol-related cause-of-death were the two outcomes. In study IV, only alcohol-related admission to hospital was the outcome.

Alcohol-related admission was defined as ever been admitted to psychiatric care with an alcohol-related diagnosis. The diagnosis was set according to the Swedish versions of the International Classification of Disease in practice at the time (ICD-8, ICD-9 and ICD-10). Common diagnoses in the study population were habitual excessive drinking, alcohol abuse and dependence syndrome due to use of alcohol. The full description of the diagnoses are found in the appendix.

Alcohol-related death was defined as having either an underlying or contributing cause of death related to alcohol. The same list of possible alcohol-related diagnoses from the different Swedish versions of ICD-codes was used for defining an alcohol-related hospital admission (appendix 1).

3.1.5.2 Alcohol consumption

In study II, alcohol consumption, measured as both total alcohol intake and pattern of drinking, were the outcomes. Information on the both outcomes was collected at conscription.Total alcohol intake was expressed in four groups of alcohol consumption level, measured in grams of 100% alcohol consumed per week: 1) Light consumers (1-100g/week), 2) Moderate consumers (101-250 g/week), 3) High consumers (>250g/week) and 4) Abstainers.

Pattern of drinking was described as either binge drinking or not, where the consumption of more than a bottle of wine or more than 35 cl. of spirits on any single occasion was considered binge drinking.

3.1.6 Record linkages

In Sweden, all Swedish citizens are assigned a personal identification number (PIN) at birth, which makes linkages between records possible. In the four studies of this thesis, following registers were used:

The National Patient Register

The National Patient Register is held by the National Board of Health and Welfare. The register is mandatory for all care-givers providing hospital or specialized care. The aim of the register is to provide statistics regarding health data and carries information from 1964 and onwards, and since 1987 it is considered to have full coverage. The quality of the register is generally high, although there are variations between regions and different periods of time (143)

The Cause of Death Register

The Swedish Cause of Death register is held by the National Board of Health and Welfare. It contains information regarding all individuals who at their time of death, were residing in Sweden. Every year, the register is compared to the number of deaths reported to the Swedish Tax Agency, and whenever information regarding cause of death is missing, this is asked for from the care giver who was responsible for the death certificate. Still, every year there cases of missing data, although the number, historically, has been very small (144).

The National Population and Housing Censuses

National Population and Housing Censuses were made in Sweden between the years 1960-1990. The register is held by Statistics Sweden and has provided with information regarding for example, population in the whole country, or in communes by age and sex, but also information regarding income and education on an individual level (145).

The Longitudinal Databases of Education, Income and Occupation (LOUISE/LISA)

The data bases LOUISE/LISA are held by Statistics Sweden. The longitudinal Database of Education, Income and Employment (LOUISE) is a longitudinal register which holds information regarding, e.g. education, income and occupation. It was started in the middle of the 1990's by Statistics Sweden. Further information regarding different measures of health was asked for, so the new Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) was built, carrying more information regarding, for example, sick and parental leave, than the data base LOUISE (146).

The Swedish Survey of Living Conditions

The Swedish Survey of Living Conditions (ULF) was started in 1975 with the general aim of collecting information regarding how the welfare is distributed within the population. From the start, until 2007, about 7 500 individuals have been selected randomly to participate in the survey every year. Included were between the years 1975-1979, individuals in the ages 16-74, and later, 1980-2001, ages 16-84 and after the year 2002, no upper age limit, who were Swedish residents. The response rate in the survey has been about 80% (147).

3.2 ETHICAL APPROVALS

Ethical approval for all included studies was granted by the Regional Ethical Review Board (EPN), Stockolm, Sweden. The approvals were for study I and II: dnr 2004/5:9-639/5 with amendment 2008/323-32, and for study III and IV: dnr 04-594/5 with amendment 2007/1070-32.

3.3 STATISTICAL METHODS

3.3.1 IQ and alcohol-related disease and death

In study I, studying the association between IQ and alcohol-related admission to hospital and death, IQ-test results were grouped into a nine-point standard scale, a so called stanine scale with a mean of five and a standard deviation of two, and modelled as a continuous variable. Cox proportional hazard model was used, yielding hazard ratios (HR) with 95% Confidence Intervals, both in the univariate and the multivariate models. The proportional hazard assumption was examined graphically. Results were presented as increase in hazard ratios with 95% Confidence Intervals per point decrease in group of stanine IQ-test result.

The full follow-up period was 1971-2007, but in a second analysis, including socio-economic position as adult, start for follow-up was 1991. Individuals with a previous alcohol-related diagnosis, were then excluded from the analysis in order to avoid reverse causality as well violate the assumption of a population at risk.

Adjustments were made for the following variables (data source within parenthesis):

1) Early life circumstances:

-Socioeconomic position as a child (National Population and Housing Census)

- Father's drinking habits (Conscription)

2) Mental health, social adjustment and behavioral factors measured at age 18

- Psychiatric diagnosis (Conscription)

- Contact with police and child care (Conscription)

- Low emotional control (Conscription)

- Daily smoking (Conscription)

- Risky use of alcohol (Conscription)

3) Adult social position

- Attained education (LOUISE)

- Income (LOUISE)

- Socioeconomic position (National Population and Housing Census)

In study III, Cox proportional hazard model was used to assess the association between IQ-test results and alcohol-related hospital admission and death. IQ-test results were grouped into stanines and modelled as a continuous variable. Analyses was made both for the whole study population and stratified by gender. Results were presented as increase in hazard ratios with 95% Confidence Intervals per point decrease in group IQ-test result.

Two follow-up time periods were used in the analyses. The first started in 1973 and 1978 for the two different cohorts, and the second in 1981 and 1986, respectively. End of follow-up was 2006 for alcohol-related hospital admission and 2005 for alcohol-related death. A mediation analysis according to Baron and Kenny was performed, investigating the mediating role of social position as adult (148). A bootstrap method was used to assess proportion of excess risk explained by socioeconomic position as adult with 95% Confidence Intervals. An interaction term was introduced in one of the analysis, to investigate the moderating effect of gender in the association.

Adjustments were made for the following variables (data source within parenthesis):

- Father's and mother's education (UGU data base)
- Father's and mother's socioeconomic position (National Population and Housing Census)
- Father or mother with alcohol-related diagnosis (National Patient Register)

- Divorced parents (National Population and Housing Census)
- Socioeconomic position as adult (National Population and Housing Census)

3.3.2 Alcohol consumption

In study II, investigating the association between IQ-test results and total alcohol intake and pattern of drinking, prevalence proportions were calculated for both outcomes across the groups of the IQ-test results (nine groups). Multinomial regression analysis, univariate and multivariate, was used to investigate the association between IQ-test result and the variable total alcohol intake during one week, grouped into four groups. Logistic regression, univariate and multivariate, was used to assess the association between IQ-test results and pattern of drinking, modelled as a dichotomous variable. Results were presented as increase of odds ratios (OR) with 95% Confidence Intervals per decrease in group IQ-test result.

Multinomial logistic regression was also used to explore the association between IQ-test score and frequency of consumption. In a sub-sample consisting of 146 individuals later in life, the association between IQ-test results modelled as a continuous variable and groups of total alcohol intake was examined. Analysis was also made for the different sub-tests of the IQ-test result and the two outcomes. Furthermore, a sensitivity analysis was performed to investigate the correlation between the continuous measures of IQ-test results and total alcohol intake.

Adjustments were made for the following variables (data source within parenthesis):

- Childhood socioeconomic position (National Population and Housing Census)
- Father's drinking habits (Conscription)
- Psychiatric symptoms present at conscripton (Conscription)
- Low emotional control (Conscription)

3.3.3 School grades and alcohol-related disease and death

In study IV, descriptive statistics of the exposure, outcome and co-variates were presented. The association between school grades and alcohol-related hospital admission to psychiatric care was investigated using logistic regression. Results from both the unadjusted and the adjusted analyses were presented in odds ratios (OR) with 95% Confidence Intervals. Average point school grade was grouped in standard deviations (four groups) and modelled as a categorical variable, with the highest grade point average group as a reference. Grade point average for the whole study population, as well as for women and men separately, was

computed. Analyses investigating the association of interest were made for the whole study population, as well as stratified by gender.

Adjustments were made for the following variables (data source within parenthesis):

- Father's and mother's educational level (National Population and Housing Census)
- Economic difficulties during childhood (LOUISE/LISA)
- Socioeconomic status as a child (National Population and Housing Census)
- Father or mother with alcohol-related diagnosis (National Patient Register)

4 RESULTS

4.1 STUDY 1

In our study population of Swedish, male conscripts, we found an association between IQ measured at conscription and later risk of alcohol-related admission and death. The association was inverse, and graded with an increasing HR of 1,29 (95%C.I.=1,26-1,31) for each step decrease in group of IQ-test score result, in the unadjusted analysis for alcohol-related admission and 1,36 (1,33-1,40) for alcohol-related death. The total number of cases of alcohol-related admission was 2 395 (prevalence ca 5%) and for alcohol-related death, we found 367 cases (prevalence ca 1%).

When adjusting for childhood circumstances (childhood socio-economic position and father's drinking habits), the association was not attenuated for any of the outcomes. After adjustment for factors measured at age 18 (psychiatric diagnosis at conscription, previous contact with police and child care, emotional control, smoking and risky use of alcohol), the HR was lowered for both outcomes. In our second time period analysis, where the aim was to investigate the association in middle-age when the individuals had reached a certain profession, level of education and income, the gradient was still present for the both outcomes.

When adjusting for these markers of socio-economic position, the OR was lowered markedly for both alcohol-related admission and alcohol-related death. Our interpretation of this finding was that socio-economic position is an important factor in the association, which calls for further investigation in order to understand the mechanism in our found association.

In conclusion:

- Inverse, graded associations were found between IQ-test results and alcohol-related admission and death
- Socio-economic position as adult could be an important factor for the association

4.2 STUDY 2

We found in this study of Swedish, male conscripts that for every step decrease in group of IQ-test results, there was an increased OR of 1,20 (95%C.I.=1,17-1,23) to be a high consumer versus being a light consumer, and an OR of 1,09 (95%C.I.=1,08-1,11) for being a binge drinker in comparison to not be a binge drinker. There was also an increased OR for being a moderate consumer versus a light consumer, with an OR of 1,07 (95%C.I.=1,06-1,08) per step decrease in group IQ-test result. For abstainers versus light consumers, we did not find any statistically significant results, except when adjusting for father's alcohol habits, when a

small increased OR of 1,03 (95%C.I.=1,01-1,05) was found per step decrease in group of IQ-test result.

For the outcome total alcohol intake, adjustment for emotional control and psychiatric symptoms diagnosed at conscription attenuated the association, which was not the case for the variables childhood socio-economic position and father's alcohol habits. For the outcome binge drinking, the inclusion of all co-variates lowered the OR, where they did not have an effect one by one. The prevalence of high consumers was 3%, moderate consumers 20%, light consumers 72%, and abstainers 6% in our study population. The prevalence of binge drinkers was 13%.

In conclusion:

- Low IQ-test results were found to be associated with both a higher alcohol total intake and a binge drinking pattern of consumption
-

4.3 STUDY 3

In this study of 21 809 Swedish men and women, we found a total of 677 alcohol-related admissions for psychiatric care (prevalence 3%) and 144 cases of alcohol-related death (prevalence 0,7%). In the whole population, an increased HR of 1,23 (95%C.I.=1,18-1,29) was found for alcohol-related admission to hospital per decrease in group of IQ-test result, and for alcohol-related death, the estimate was 1,28 (95%C.I.=1,07-1,53) in the unadjusted analysis. In our stratified analysis by gender, women had an increased HR of 1,15 (95%C.I.=1,05-1,27) for being admitted for an alcohol-related diagnosis per decrease in group of IQ-test results , where the corresponding figure for men was1,27 (95%C.I.=1,21-1,33). For alcohol-related death, women, again, had a lower HR, than men in the stratified analysis. However, when testing for interaction, no significant difference was found between the genders. We performed a mediation analysis, which indicated that socio-economic position as adult was a partial mediator for alcohol-related admission to hospital, and a complete mediator for alcohol-related death, although the results were less reliable for women due the low number of cases.

In conclusion:

- Inverse, graded associations between IQ and alcohol-related admission and alcohol-related death was found
- The association did not seem to interact with gender
- Socio-economic position as adult was found to at least partially mediate in the found associations

4.4 STUDY 4

There was a total of 3 323 cases of alcohol-related admission for psychiatric care in the study population (prevalence 2%). An OR of 7,63 (95%C.I.=6,50-8,94) between the lowest in comparison with the highest group of GPA was found, in the unadjusted analysis, for being admitted with an alcohol-related diagnosis for psychiatric care, in the whole study population. Among women, there were 1 270 cases of alcohol-related hospital admission, and the corresponding number for men was 2 053. The OR:s for women and men, when comparing the group of lowest with the highest GPA, were both similar with the estimate for the whole study population: 7,46 (95 %C.I.=6,00-9,27) for women and 7,19 (95%C.I.=5,63-9,18) for men. For both men and women, a gradient was observed, where the OR for being admitted with an alcohol-related diagnosis, increased by step decrease in group of GPA. Adjustment for parents' education, socio-economic position, admission for alcohol-related diagnosis and receipt of welfare lowered the OR somewhat for both genders, for the group with lowest GPA. Interestingly, when adjusting for IQ-test results in a sub-sample, the estimates for the different groups of GPA remained almost the same.

In conclusion:

- A graded, inverse association was found between grade point average and alcohol-related admission to psychiatric care
- The association was found for both women and men
- Adjusting for IQ did not attenuate the association

5 DISCUSSION

5.1 MAIN FINDINGS AND PREVIOUS RESEARCH

The main results of study I and III, which showed an inverse, graded association between IQ-test results and alcohol-related disease and death, are in line with some of the previous studies on cognitive ability and alcohol-related outcomes (122-124). However, an opposite association, where high results on cognitive ability tests was associated with higher risk of problems with alcohol has also been found previously (113, 119), as well as a non-significant association between cognitive ability and an alcohol-related outcome, analyzing Swedish data (114). A possible explanation for the differing results between studies could be that the choice of outcome matters when investigating the association with cognitive function. One could also expect the association to differ by time period and country, due to differing norms and culture regarding alcohol consumption.

The conclusion of social position as adult as a possible mediator, has also been suggested by previous studies (121, 124). It is reasonable to consider social position as adult as an important factor in the investigated association, as it is a well-established determinant of health. The relative importance of intelligence, achieved level of education and socio-economic position for alcohol-related outcomes is still to be evaluated further, and it may also differ depending on type of alcohol-related outcome. Although probably not the only factor involved in the explanation of how intelligence and health is associated, we have provided support for the suggested role of adult socioeconomic position as one possible mechanism.

Our study III did not provide any evidence of a difference between genders, which is in line with a previous study, using hang-over as an outcome (121). (121). In three other studies, where the association per se was the opposite from what we found in ours (study III), no difference between the genders was found (113, 119, 149). This could be understood as if there is an association, the direction is the same for both genders. This is interesting, as alcohol behavior and the consequences of alcohol consumption are considered to be gender specific.

For study II, our findings that a low IQ-test result was associated with both a total higher alcohol intake and a binge drinking pattern of drinking, diverge from what has previously been shown. Low verbal ability in comparison between twins, has been shown to be associated with less frequent drinking and intoxication, later in life (118), which is somewhat in concordance with another study, where low cognitive ability was associated with being an abstainer (150). Yet another study has shown a positive association between IQ-test results and an alcohol-related outcome, which included symptoms of alcohol abuse/dependence and average quantity consumed in past 12 months (150). Yet another study has shown a positive association between IQ-test results and an alcohol-related outcome, which included symptoms of alcohol abuse/dependence and average quantity consumed in past 12 months

(149). Again, probably choice of outcome matters for the results in the analysis of the association between intelligence and alcohol consumption, as well as differences between study population due to, for example, societal and cultural norms.

Regarding study IV, our findings that a high school performance is associated with lower risk of alcohol-related outcomes, were consistent with some previous research (130, 131, 151). A non-significant association has however also been reported (129). And, as noted before, the lack of difference between genders found in our study, is in accordance with one previous study (131), but, in another the lower risk of an alcohol-related outcome was found among highly achieving boys, but not among girls (130). The recently published study from Sweden, using the same, but larger material, found that the risk was stronger among males, than among females (132). In our study, we did not find support for the importance of IQ-test results in the association between school grades and alcohol-related hospital admission. The investigated association could still be confounded by other variables that we did not have the opportunity to adjust for, such as for example, motivation.

In none of the four studies, measures of childhood conditions, such as socio-economic position as a child or having a parent with an alcohol-related diagnosis, seemed to be a confounder in the investigated associations. Rather, variables representing mental health or behavioral factors measured in late adolescence, were observed to attenuate the investigated associations, where available.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Study designs

In epidemiology, the object of a study is to attain an estimate of a disease frequency measure, effects or attributable fractions, either as a single measure or in comparison with others (152). To achieve these measures, both experimental and non-experimental methodology is used. However, the possibility to make use of experiments within epidemiology is often restricted, partly due to the constraints for manipulation of conditions, partly due to the ethics involved in exposing individuals for potentially harmful situations. Therefore, non-experimental, or observational, studies are common within epidemiology (153). In this thesis, cohort and cross-sectional study designs are used.

5.2.1.1 Cohort studies (I, III, IV)

Studies I, II and IV in this thesis are closed, retrospective cohort studies.

A cohort study is an observational study in which incidence of disease is measured and, or, compared between groups of individuals, followed over time, which share a common feature. This feature could be either an experience, or a condition, such as being born the same year (birth cohort), or been diagnosed with a certain disease. In order to take part of a cohort, one needs to be at risk for the event studied. A cohort study may be *open* or *closed*, referring to

whether new members are allowed into the cohort or not, after start of study. It may also be *prospective* or *retrospective*, where in a prospective study, the information on exposure is collected before start of study and the time at risk is concurrent with study time. In a retrospective study, also called *a historical cohort study*, time at risk is before study time, and information about the individuals is retrieved after study start.

5.2.1.2 Cross-sectional study (II)

Study II in this thesis, is designed as a cross-sectional study.

A cross-sectional study typically collects information on exposure and disease at the same occasion and it includes all individuals in a population at that time, without considering exposure or outcome status. Two problems have been identified regarding cross-sectional studies: first, it is difficult to infer causality due to lack of information regarding temporality, and second, long-duration cases will be overrepresented, and, equivalently, short-duration cases will be underrepresented in a cross-sectional study. This is called length-biased sampling (153).

5.2.2 Accuracy and validity

In an epidemiologic study, the aim is to retrieve as accurate estimate possible of the measurement of interest. Accuracy implies little error in the estimation process. Errors in an epidemiologic study may be of two kinds: systematic and random. Systematic errors are errors which are not dependent on study size and are the results of mainly two kinds of biases (selection and information) and confounding. Random errors are dependent on study size and are inversely related to size of study population. An estimate with low systematic error, is said to be valid, and an estimate with low random error, is said to be precise.

The validity of a study relates both to the accuracy in the found estimate with regard to the individuals within study population (internal validity) and to the individuals outside the study population (external validity).

5.2.2.1 Systematic errors

There are in general three main types of systematic error in an observational study: selection bias, information bias and confounding.

Whenever there is a difference in the investigated association between the individuals that take part in a study and those who do not, a systematic error called *selection bias* has come about. How the association of interest appears for the individuals which are not participating, is not known, why selection bias cannot be observed, but inferred (152).

In study I, II and IV, total national birth cohorts are the study populations. For study I and II where the Swedish conscripts cohort is the study population, information was collected for

about 97% of the study population (154). Among those 1,2% did not answer the questionnaire regarding substance use and misuse (136). In study III, the UGU data base is used, with samples for individuals born 1948 and 1953. The drop-out for participation in the intelligence test for individuals born 1948 has been calculated to 9.0%, and for those born 1953, 6.3%., which together make a total drop-out of 7% for the whole sample used. The reason for drop-out in this population has been thought of as normal absence from school, and not having any implications for the interpretation of the results in this regard (155). For study IV, the National School Register with school grades from 9th grade was used for national birth cohorts born 1972 and 1977. The aim of the National School Register, is to include all pupils that have the completed the nine years of compulsory school.

The overall interpretation of the likelihood of selection bias in the studies comprised in this thesis, is that it is very limited.

Information bias occurs when there is error in the information collected from the study participants, which leads to misclassification of, for example, exposure or outcome. There are two kinds of misclassification, differential and nondifferential. Differential misclassification is an error that is dependent on other variables, whilst nondifferential is not. The consequences of a nondifferential misclassification, is that the estimate tends to be diluted, that is, lower than the actual estimate. A differential misclassification can lead to both an over- as well as an underestimation of an estimate (152).

Misclassification of exposure

In studies I, II and III the exposure is results of IQ-tests performed at ages 13 (study III) and 17-18 (study I, II). In study IV, the exposure is grade point average for an individual in the 9th grade, compulsory school.

In both of these exposures, it is not likely that an individual would perform above one's capacity. If underachieving, it may be the result of previous alcohol use on the IQ-testing or setting of grades, and the association would then be a consequence of reverse causality, and a differential misclassification with a probable overestimation of the estimate would be present.

Misclassification of outcome

In studies I, III and IV the outcome is alcohol-related diagnosis, for hospital admission and cause of death. The inpatient register has been validated and found to be reliable for many diagnoses, unfortunately, alcohol-related diagnoses were not included (156). For the Swedish Cause of Death Register, a study has shown that 77% of the underlying cause of death within the register, was correct (157). One could speculate that, since intelligence is so closely related to education, one of the three main indicators of socioeconomic position, a high IQ would lead to a smaller risk of being diagnosed with an alcohol-related diagnosis. This would lead to an overestimation of the estimate, due to differential misclassification.

In study II, the outcome is total alcohol intake and pattern of drinking. It has been shown that answers from non-anonymous questionnaires provides underestimates of alcohol consumption (158). This is however likely to be nondifferential, thereby probably diluting the estimate.

Confounding is what occurs when the effect of the exposure on an outcome is mixed with the effect of another factor, a confounder. To be a confounding factor it has to 1) be a risk factor for the outcome, 2) associated with the exposure and 3) not affected by the exposure or the outcome. It should neither be on the causal pathway between exposure and outcome. The mistake of interpreting the mixed effect of an exposure and a confounder as an actual effect, may lead to both over- and underestimation of an effect, as well as change the direction (153). There are two methods to help deal with confounding in the analyses of data: 1) stratification and 2) the possibility to include several factors in a regression model, which results in that each factor is unconfounded by the other factors in the model.

Stratification was used in study II, III and IV in this thesis, and adjustments for co-variates selected by à priori-knowledge, were made in all four studies:

In study I, in which the association between IQ-test results in adolescence and later risk of alcohol-related admission and death was investigated, adjustments were made for several possible confounders across the life course. Factors from early life (socio-economic position as a child, father's drinking habits), information from conscription at age 18 (psychiatric diagnosis, contact with police and child care, low emotional control, daily smoking and risky use of alcohol) and adult socio-economic position (attained education, type of occupation and income). Although the adjustments made for the variables measured at age 18 did weaken the association somewhat, it was in the adjustment of adult socio-economic position, a clear reduction in the hazard ratio was seen.

In study II, where the association between IQ-test results and alcohol consumption was the focus, adjustments for socio-economic position as a child, and co-variates that were measured at conscription: psychiatric symptoms, emotional stability and father's alcohol habits, were made. Adjustments for childhood socio-economic position as a child and father's alcohol habits did not reduce the found association for the outcome total alcohol intake. When adjusting for psychiatric symptoms present at conscription and emotional control, an attenuation was observed, however. For the outcome pattern of drinking, the individual adjustment of the co-variates did not have an effect on the association. When all co-variates included, however, an attenuation was seen.

Again, in study III, where the association between IQ-test results measured at age 13 and later risk of alcohol-related hospital admission and death was the interest, socio-economic position as a child, as well as information on divorce of parents and alcohol-related admission for any parent were adjusted for in the regression models. In general, adjustment for these co-variates in the analysis of the investigated association did not markedly attenuate the found association.

For study IV, adjustments were made for educational level of both parents, as well as any parent receiving social welfare, having an alcohol-related hospital admission and an index of socioeconomic position as a child based on occupation of parent. An attenuation of the association was seen after adjustments of the stated co-variates, although not markedly.

In none of the four studies in this thesis, we had the possiblity to adjust for any genetic explanation for the found associations. In study I and II, information on psychiatric diagnosis was available, but not for studies III and IV. There is always an issue with residual confounding in observational studies, which certainly is true also for the studies presented within this thesis. The framework consisting of the four suggested mechanisms as to how intelligence and different health outcomes may be associated could be viewed as highly condensed, where more and other factors, such as personality traits and behavior, could be added to achieve a more complex picture.

Regarding the *external validity*, or the generalizability, of these four studies, it would depend on what mechanism you would expect to act in the associations between cognitive function and alcohol-related outcomes. The more biological explanation, the less you would expect the associations to vary. However, given previous divergent results for studies focused on alcohol-related outcomes, one could expect the association to differ between countries, cultures and time periods. Probably, our contribution is generalizable to populations where conditions, similar to the ones present in these four studies, are prevailing. One could argue that the findings from the generation of male conscripts born in 1949-51, as well as the results of the UGU data base, where the individuals are born 1948 and 1953, might differ from what would be expected in a society changed over time. However, the results from the national birth cohorts born 1972 and 1977, contradicts such an argument. If the association is not varying over time, it may vary by drinking culture.

5.2.2.2 Random error

The random error in a study is depending on chance, and relates to the precision of an estimate. The larger the study, the more precise estimate. To test the null hypothesis, that is, no association between exposure and outcome, a P-value is often calculated. The P-value is used to decide whether statistical significance is present, or not. In epidemiology, there has lately been a preference for presenting the confidence intervals for an estimate, instead of a P-value. Confidence intervals are calculated from the same equations as P-values, but allows for interpretation of both the strength of the association and the precision of the estimate (152).

In the four studies in this thesis, in general, the population sizes are fairly large, why the risk of random error is limited. However, for some of the stratified analyses, and when making use of sub-samples within the cohorts, the confidence intervals grow larger due to higher variability within the data, and thereby achieving less precision.

6 CONCLUSIONS, IMPLICATIONS AND FUTURE DIRECTIONS

This thesis aimed to contribute to the field of cognitive epidemiology with knowledge about the association between cognitive function, alcohol use and alcohol-related harm. We have been able to show that intelligence, measured as IQ, had an inverse association with risk for alcohol-related hospital admission and death, in our study populations. The association did not seem to be moderated by gender, and socio-economic position was found a least to partially mediate in the association. Furthermore, we were able to present results regarding the association between intelligence, measured as IQ, and two different measures of alcohol consumption, where a low IQ-test result was found associated with both a higher total intake of alcohol, and a binge drinking pattern of consumption. Adding to this, we found that school grades from the 9th grade of compulsory school were inversely associated with risk for hospitalization due to an alcohol-related diagnosis. This association was similar for both genders and did not seem to be confounded by intelligence, measured as IQ-test results.

Adjustment for several co-variates from different time points in life, attenuated the found associations to differing degrees, where especially social position as adult was found to be an important variable.

Within the field of cognitive epidemiology, the issue of the implications of the research, is a constant question. Intelligence, as well as alcohol use and its harmful consequences, are subjects which engage the public, and ethical considerations need to be included in the discussion of implications. This thesis has shown that intelligence is associated with how individuals consume alcohol. Intelligence is, however, still just one of several risk factors which contribute to the complex behavior of alcohol consumption. Societal factors, such as drinking culture and alcohol policies certainly influence extent of alcohol-related harm, as well as other individual factors, known from the vast literature of alcohol research. Also, the effect of schooling seem to have a separate effect from intelligence on risk of alcohol-related disease. Although just one risk factor of many others, it should not be neglected. As shown, intelligence is important for an individual in many aspects of life, and further understanding about how and why intelligence is related to alcohol misuse and health in general may help in the everyday work of a clinician, or in preventive measures where, for example, demands on cognitive function may be high.

Socioeconomic position as adult has proven its relevance also within the field of cognitive epidemiology. How intelligence, education, socioeconomic position and alcohol-related outcomes are associated will surely continue to intrigue and inspire to further research.

In the studies included in this thesis, we did not find any gender differences in the associations. This was somewhat surprising, given the well-established, although maybe diminishing, differences between genders in alcohol consumption. It would be interesting to

see more studies, from other populations, investigating gender differences in the associations investigated in our Swedish study populations.

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9 APPENDIX

ICD-10	Code
Mental and behavioural disorders due to use of alcohol	F10
Acute intoxication	F10.0
Harmful use	F10.1
Dependence syndrome	F10.2
Withdrawal state	F10.3
Withdrawal state with delirium	F10.4
Psychotic disorder	F10.5
Amnesic syndrome	F10.6
Residual and late-onset psychotic disorder	F10.7
Other mental and behavioural disorders	F10.8

Unspecified mental and behavioural disorder	F10.9
Alcohol-induced pseudo-Cushing's syndrome	E24.4
Alcoholic gastritis	K29.2
Degeneration of nervous system due to alcohol	G31.2
Maternal care for (suspected) damage to fetus from alcohol	O35.4
Alcoholic cardiomyopathy	I42.6
Alcohol rehabilitation	Z50.2
Toxic effect of alcohol	T51
Ethanol	T51.0
Methanol	T51.1
2-Propanol	T51.2
Fusel oil	T51.3
Other alcohols	T51.8

Alcohol, unspecified	T51.9
Alcoholic polyneuropathy	G62.1
Alcoholic liver disease	K70
Alcoholic fatty liver	K70.0
Alcoholic hepatitis	K70.1
Alcoholic fibrosis and sclerosis of liver	K70.2
Alcoholic cirrhosis of liver	K70.3
Alcoholic hepatic failure	K70.4
Alcohol abuse counselling and surveillance	Z71.4
Alcohol use	Z72.1
Alcoholic myopathy	G72.1
Alcohol-induced acute pancreatitis	K85.2
Alcohol-induced chronic pancreatitis	K86.0
Evidence of alcohol involvement determined by blood alcohol level	Y90

Blood alcohol level of less than 20 mg/100 ml	Y90.0
Blood alcohol level of 20-39 mg/100 ml	Y90.1
Blood alcohol level of 40-59 mg/100 ml	Y90.2
Blood alcohol level of 60-79 mg/100 ml	Y90.3
Blood alcohol level of 80-99 mg/100 ml	Y90.4
Blood alcohol level of 100-119 mg/100 ml	Y90.5
Blood alcohol level of 120-199 mg/100 ml	Y90.6
Blood alcohol level of 200-239 mg/100 ml	Y90.7
Blood alcohol level of 240 mg/100 ml or more	Y90.8
Presence of alcohol in blood, level not specified	Y90.9
Evidence of alcohol involvement determined by level of intoxication	Y91
Mild alcohol intoxication	Y91.0
Moderate alcohol intoxication	Y91.1

Severe alcohol intoxication	Y91.2
Very severe alcohol intoxication	Y91.3
Alcohol involvement, not otherwise specified	Y91.9
ICD-9	
Alkoholpsykoser	291
Delirium tremens	291A
Psychosis Korsakow	291B
Annan alkoholbetingad demens	291C
Alkoholhallucinos	291D
Patologiskt alkoholrus	291E
Patologisk svartsjuka, Alkoholbetingad paranoia	291F
Annan specificerad alkoholpsykos	291W
Alkoholpsykoser, ospecificerade. Kronisk alkoholism med psykos	291X

Alkoholberoende. Alcoholismus. Kronisk alkoholism	303
Alkoholmissbruk	305A
Alkoholpolyneuropati	357F
Alkoholbetingad kardiomyopati	425F
Gastrit orsakad av alkohol	535D
Alkoholfettlever	571A
Akut alkoholhepatit	571B
Levercirros orsakad av alkohol	571C
Ospecificerad leverskada orsakad av alkohol	571D
Förhöjd alkoholnivå I blodet	790D
Toxisk effect av alkohol	980
Toxisk effet av etylalkohol	980A
Toxisk effect av metylalkohol	980B
Toxisk effet av isopropylalkohol	980C

Finkelolja	980D
Andra alkoholer	980W
Toxisk effect av alkohol, ospecificerad	980X