The Danish longitudinal study of alcoholism 1978-2008

A clinical high-risk study

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THE 7 ORIGINAL PUBLICATIONS ARE:

I. Knop J, Teasdale TW, Schulsinger F, Goodwin DW. A prospective study of young men at high risk for alcoholism: School behaviour and achievement. J Stud Alc 1985;46:273-278.
II. Schulsinger F, Knop J, Goodwin DW, Teasdale TW, Mikkelsen U. A prospective study of young men at high risk for alcoholism: Social and psychological characteristics. Arch Gen Psychiatry 1986,43:755-760.
III. Knop J, Goodwin DW, Jensen P, Penick EC, Gabrielli WF, Teasdale TW, Mednick SA. A 30-year follow-up study of the sons of alcoholic men. Acta Psychiatr Scand 1993:Suppl.370:48-53.
IV. Knop J, Penick EC, Jensen P, Nickel EJ, Gabrielli WF, Mednick SA, Schulsinger F. Risk factors that predicted problem drinking in Danish men at age thirty. J Stud Alc 2003;64:744-755.
V. Knop J, Penick EC, Mortensen EL, Nickel EJ, Gabrielli WF, Jensen P, Mednick SA. Prediction of mortality in Danish men at high and low risk for alcoholism. A forty year follow-up. Acta Psychiat Scand 2004;110:476-482.
VI. Knop J, Penick EC, Nickel EJ, Mednick SA, Jensen P, Manzardo AM, Gabrielli WF. Paternal alcoholism predicts the occurrence but not the remission of alcoholic drinking: A 40 year follow-up. Acta Psychiat.Scand 2007;116:386-393.
VII. Knop J, Penick EC, Nickel EJ, Sullivan MA, Murtaza S, Mortensen EL, Jensen P, Gabrielli WF. Childhood conduct disorder and ADHD as independent predictors of male alcohol dependence at age 40. J Stud Alc Drugs 2009;70:169-177.

1. BACKGROUND

1.1 THE GENE-ENVIRONMENT ISSUE IN ALCOHOLISM

It is an old observation that alcoholism runs in families. This observation has provided speculation throughout the centuries about a potential genetic etiology. However, the running-in families phenomenon does not necessarily imply inheritance, because the majority of children who become alcoholic have been raised by their biological parents. A variety of environmental and developmental stressors have been proposed as significant etiological factors for drinking problems later in life. At present, it is a predominant hypothesis that both biological/genetic, psychological and social factors (in different combinations) contribute to the development of alcoholism [1].

1.2 FAMILY STUDIES

In an extensive survey of the scientific literature on familial alcoholism, 39 family studies on alcoholism were reviewed over the past 45 years covering a total of 6,251 alcoholic and 4,083 non-alcoholic probands [2]. The prevalence rates of alcoholism was found to be significantly higher among relatives of alcoholics when compared to relatives of non-alcoholics (31% vs. 5%). It was concluded that the familial aggregation of alcoholism was robust. Another family study [3] also concluded that alcoholism is a familial phenomenon.

However, the traditional family study design is not suitable for the identification of etiological factors and is not able to separate genetic and environmental risk factors. New epidemiological designs have been developed during the past three decades as valuable contributions to the ongoing “nature-nurture” question, bringing us closer to an empirical understanding of significant risk factors. These designs will be discussed in the following sections.

1.3 TWIN STUDIES

Monozygotic (MZ) twins are genetically identical, and any differences between them are likely to be environmental in origin. The classic research design is to compare concordance rates of a specific disorder in MZ and dizygotic (DZ) twin pairs. A higher concordance rate among MZ twins compared to DZ twins indicates that a genetic component plays a considerable etiological role. In the study of alcoholism, several well-designed twin studies have been conducted:

Since Lennart Kaij conducted the first twin study with focus on alcoholism [4], several studies using the same twin methodology have demonstrated that genetic factors are significant for the development of alcoholism, most pronounced among males [5-11]. In spite of different study designs (utilizing clinical data, archival data and/or family history data) the overall conclusion has been that genetic factors are of major etiological importance, while environmental factors play a significant less important role.

In this connection, the study of disconcordant MZ twins should be mentioned as a reliable methodology estimating the influence of early environmental/familial factors.

While MZ twins do have identical genetic “equipment”, they also share environment during childhood, upbringing, schooling

etc. It is characteristic that twins have a delayed growth rate in late pregnancy and a lower birth weight and higher rate of birth complications when compared to singletons. These perinatal deficits make twins a highly selected group of children and difficult to compare with the general population.

Extension of the classic twin design by including siblings to twins is a promising additional method, in particular comparisons of twin-siblings and DZ twin pair correlations are especially useful in a gene-environment context [12].

1.4 ADOPTION STUDIES

Another way of investigating the nature-nurture question is to study individuals with alcoholism in their biological family but not in the family of upbringing. Adoption studies provide the possibility of distinguishing genetic and environmental effects, since adopted-away children receive their genes from their biological parents and environmental influences from their non-biological parents.

In the research field of alcoholism, several adoption studies have contributed to the ongoing discussion of the interaction of genetic and environmental factors for the development of alcoholism later in life. In spite of different designs, selection of subjects and source of information, a predominant conclusion is that genetic influence seems to play an important etiological role for alcoholism in adulthood, most characteristic among males [13-18].

An adoption study on alcoholism conducted by the same Danish-American research group as the present study shall be described in more detail:

The biological parents of all adoption cases 1924-47 in Copenhagen (n = approx. 5000) were screened in the Danish Psychiatric Register [19] with regard to psychiatric discharge diagnoses. *First phase* of the study comprised diagnostic interviews with 55 adopted-away sons of alcoholic fathers compared with 78 matched adoptees without parental alcoholism. Only two variables distinguished the two groups: Rate of alcoholism (18% vs. 5%) and divorce (27% vs. 9%) [20]. *Second phase* included interviews with biological brothers to the adopted-away sons who stayed home together with the alcoholic biological fathers. The main finding was that sons raised by their alcoholic parents had the same increased risk of becoming alcoholics themselves as compared with their adopted-away biological brothers [21]. *Third phase* was using the same design selecting adopted-away daughters of alcoholic vs. non-alcoholic biological parents. The diagnostic interviews were conducted by the author. We found a low rate of alcoholism/serious drinking problems (2%) and affective disorder (approx. 4%) in both groups, indicating that genetic factors may play a minor role for the development of female alcoholism [22, 23].

The main findings from these adoption studies are that sons of alcoholics have a 3- to 4-fold risk of developing alcoholism themselves. This increased risk seems to be partly independent of the upbringing environment, indicating that a considerable genetic component may play a significant role in the development of alcoholism later in life. However, these important results could not be replicated in the adoption study on female offspring of alcoholic fathers. Several of the other adoption studies mentioned above came to the same conclusion that the genetic vulnerability seems to be most predominant in males.

Unfortunately, the demographic pattern of adoptions in Denmark has changed radically throughout the past decades: The vast majority of adoption cases involve non-Danish biological parents, mostly from South-Eastern Asia, indicating that parental psychopathology, socio-economic status etc. cannot be examined reliably anymore. Another limitation in following up adoptees in Denmark is the fact that the Ethical Scientific Committee does not approve person-to-person research interviews anymore.

1.5 HALF SIBLING STUDIES

Examination of half-siblings of alcoholic parents compared to half-siblings of non-alcoholic parents is another methodology contributing to the nature-nurture question. Schuckit et al. [24] examined 151 half-siblings of 61 alcoholic parents. 65% of the alcoholic half-siblings had an alcoholic biological parent compared to 20% of the non-alcoholic half-siblings. The result reflects that a genetic component plays a considerable role for the development of alcoholism.

1.6 CONTEMPORARY GENETIC RESEARCH

The complexity of etiological factors in alcoholism has received new attention due to the recent complete mapping of the human genome. A significant correlation between the A1 allele of the dopamine D2 receptor and alcoholism has been reported [25], but never replicated with enough consistency. Another study group found a correlation between the gene GABRG 3 on chromosome 15 and risk for alcoholism [26]. Several other studies have proposed other one-to-one relationships between complex alcoholic behaviour and specific genes variances and certain locations of activity in the CNS-system. Major aspects of these genetic-environmental research questions have been discussed and clarified by Hill [27].

However, the single-gene view of genetics in the alcoholism research field has been replaced by the realization of complexity, both of genetic and environmental origin. It is most likely that candidate genes have influence on intermediate characteristics, the so-called endophenotypes, that affect the risk of heavy drinking/alcoholism [28]. It is hypothesized that these endophenotypes interact with both genetic and environmental factors. Several factors have already been proposed as putative endophenotypes: Social anxiety disorder [29] and novelty seeking behaviour [30]. An extensive review of the interplay between genetic factors and the increasing range of endophenotypes has recently been published [31]. Another recent contribution is describing the results from the first genome-wide association study of alcoholism including a screen of the whole genome in an effort to identify low frequency genetic variants [32]. The contribution of genetic epidemiology is to "translate" advances from molecular genetics into epidemiological/clinical research and public health initiatives [33].

1.7 CONCLUSIONS

Family studies on alcoholism have demonstrated a significant familial aggregation. However, the running-in-family phenomenon *per se* does not contribute to the etiological gene-environment question. Both twin-, adoption- and half-sibling studies mentioned in this section point to a considerable genetic component in the development of alcoholism. This fact seems to be most predominant among males, while female alcoholism may have a different and more environment-based etiology [34].

Undoubtedly, antecedent development deficits, stressors of different origin, physiological reactions to drinking, psychological risk factors, familial problems, learning disabilities, cognitive handicaps etc. in different combinations are important risk factors for the development of alcoholism in adulthood. Conse-

quently, it is important to keep the interdisciplinary research approach in mind.

Most important is to develop longitudinal research designs utilizing well-defined high and low risk groups, where the data collection is initiated before effects of increasing alcohol problems develop to identify antecedent risk factors. Over the time, this is the only reliable scientific basis for developing rational prevention programs both for the population as a whole and also at the individual level.

2. THE HIGH-RISK PARADIGM

2.1 INTRODUCTION

The majority of clinical and etiological alcohol research is based on retrospective and/or cross-sectional designs. Findings from such studies, no matter how promising, cannot be easily interpreted in an etiological context, because it is impossible to know whether they reflect antecedent, consequential or epiphenomenological factors. To identify characteristics (medical, psychological or social) that precede alcoholism, it is necessary to obtain non-retrospective, premorbid data. This indicates that a prospective longitudinal study design is necessary. Alcoholism seems particularly amenable to such studies for two reasons. Firstly, it has a rather specific risk period early in life, so that studies can be initiated and completed within a reasonable span of time (2-3 decades). Secondly, alcoholism is generally regarded as a chronic condition, suggesting that a follow-up at any point within the risk period has a high probability of detecting alcoholic drinking pattern, if it has developed.

2.2 LIMITATIONS

A limitation of the prospective follow-up method is that an impracticably large number of subjects may be required to obtain an outcome rate of affected individuals sufficient for statistical analyses. In the case of alcoholism, the estimated prevalence rate in the general Danish population is approx. 6-10% among males and 4-6% among females [35].

This limitation, however, can be mitigated by studying populations "at risk" in which the outcome is considerably higher than that of the general population. The adoption- and twin studies described in the previous chapter indicate that offspring (in particular biological sons) of alcoholics represent a group at a well-defined increased risk for becoming alcoholics themselves. These studies suggest that between 20 and 25% of sons of alcoholics will themselves become alcoholics. Therefore, such individuals are considered at "high risk" regarding future development of alcoholism. A longitudinal follow-up study of individuals defined premorbidly as high and low risk is called the high-risk paradigm.

Other problem areas in longitudinal research are:

Attrition: A well-known limitation of prospective longitudinal research is an increasing rate of attrition throughout the follow-up examinations. An essential question is whether the most affected individuals (i.e. the alcohol dependent subjects) are concentrated in the group of non-participants. It has recently been shown that non-participants have a worse overall health profile compared with participants in a Danish long-term study [36]. Several reports have established evidence for special attrition problems in psychiatric follow-up studies [37-39]. It is a well-known fact that alcoholic and/or subjects with antisocial personality disorder (ASPD) belong to the most difficult group of individuals to get motivated for participation [40, 41]. There are several types of non-participation influencing the attrition rate: Non-response to any application, refusal, emigration, serious illness and death. In our study we have analyzed differences between participants and non-participants (see paper IV) by searching them for psychiatric discharge diagnoses in the Danish Psychiatric Central Register. However, this search is limitated by the fact that only a minority of Danish alcoholic patients have ever attended a psychiatric ward.

Costs and time consumption: Depending of the number and intervals of follow-up assessments, large costs must be included in the considerations already in the preparing phase of the study. Concerning staff recruitment it is desirable if the original staff members in the study is continuing their work throughout the long course. In other words: It is preferable if the researcher is not very much older than the subjects, so he/she can reap the benefit of the long research process themselves.

Obsolete research instruments: A serious problem in long term follow-up research is that measurements and diagnostic instruments from the initial phase of the study may seem outdated/obsolete decades later. Therefore, it is recommendable to keep theories and hypotheses fairly general just from the very beginning of the study. The original choice of instruments should be eclectic/multidisciplinary, and not dominated by one specific theoretical orientation. This aspect is particularly important in the field of alcoholism, which is generally regarded as a complex disorder associated with biological, psychological and social etiologies. The integrated approach has become the predominant conceptual framework to researchers and clinicians alike.

Nevertheless, the described limitations in longitudinal follow-up research are clearly compensated by the strengths concerning 1) the generation of causal hypotheses, and 2) the contribution to the development of methods of early detection and prevention of subsequent illness. The obvious advantage of studying longitudinal outcome data is that the originally collected information cannot be attributed to the effects of the disorder under study, i.e. alcoholism and/or its clinical complications.

2.3 PREVIOUS STUDIES

The high-risk paradigm was introduced in psychiatric research approx. 50 years ago by Sarnoff Mednick and Fini Schulsinger [42, 43]. Initially, they examined a group of Danish children (mean age approx. 13 years in 1962) of schizophrenic mothers and a matched group of offspring of non-schizophrenic parents before any of them had developed clinical signs on psychiatric illness. Subsequent follow-up examinations took place in 1967, 1973, 1980 and 1999 [44-48]. The study is still in progress, and another follow-up assessment is planned in the near future.

Among other psychiatric disorders, alcoholism has also been the object of several longitudinal high-risk studies focusing on a broad range of measures covering biochemical, neurophysiological, metabolic, neuropsychological defects and psychological, social and behavioural risk factors. [49-53]. The most consistent risk factors identified in these early studies are: An alcoholic father, impulsivity and dyssocial behaviour. Rydelius conducted a 20 year follow-up study in Sweden of 229 offsprings of alcoholic fathers and 163 matched controls [54]. This register-based study focused on social adjustment and health status of the children 20 years later in life. The probands were more in need for social assistance, had more contact with temperance institutions, more criminality and "consumption" of psychiatric wards and out-patient-clinics when compared to control subjects. This increased risk seemed to be independent of the external environment [55].

Vaillant conducted a 60 year longitudinal follow-up study in USA of 456 socially disadvantaged Boston male adolescents (core city

sample) and 268 matched former Harvard-undergraduates (college sample). The aim of the study was to examine the course of male alcoholism over lifetime. In both groups alcoholism was rare at age 70, primarily due to premature death or stable abstinence. Alcohol abuse could persist for decades without remission, death or progression to alcohol dependence. Prior alcohol dependence and AA attendance were the strongest predictors of sustained abstinence [56, 57].

Schuckit and co-workers have conducted The San Diego Prospective Study of Alcoholism since 1978. After an initial assessment of family history positive (FHP) and family history negative (FHN) offspring of alcoholic fathers, the two groups of subjects have participated in follow-up examinations at age10, 15, 20 and 25 years. A main result is that the FHP-subjects had a lower level of response on alcohol challenge compared to the FHN-group at the premorbid initial assessment. The subsequent follow-ups indicated that the premorbid levels of response had considerable predictive power [58-60].

The Pittsburgh Youth Study [61, 62] have examined if early adolescent psychopathology predicts alcohol use disorders by young adulthood. In particular, early symptoms of conduct disorder emerged as a robust predictor of increased of alcohol dependence by young adulthood.

Another longitudinal prospective study [63] found that familial density of alcoholism played a significant predictive role for adolescent alcohol initiation.

The impact of maternal drinking in pregnancy on the offspring has been examined in an Australian longitudinal cohort study. In utero alcohol exposure was associated with more alcohol disorders in the offspring at age 21 [64].

The first review of longitudinal research in the field of alcoholism was published in 1984 [65].

3. THE DANISH LONGITUDINAL STUDY OF ALCOHOLISM

3.1 INTRODUCTION

The Danish Longitudinal Study of Alcoholism was originally designed to identify premorbid predictors of alcoholic drinking that operate singly or in combination. The high-risk research paradigm was chosen to compare two groups of adolescent boys, one with and one without alcoholic fathers, on many dimensions before any of them had developed alcoholic problems. The long-term research strategy includes a premorbid assessment at age 19-20 year with subsequent follow-up examinations at age 30 and 40 years. In addition, the study group has had access to data covering pre-, peri- and postnatal variables and information from the subjects' achievement in school. Also archival data including medical and psychiatric admissions, criminality and causes of death have been available as a valuable supplement in case of lacking information due to non-participation in the follow-up waves.

3.2 AIMS OF THE STUDY

1. To discover premorbid measures from multiple domains that distinguished high-risk sons of alcoholics from low risk sons of non-alcoholics, before any of them had developed alcoholic problems.
2. To determine which of the premorbid risk markers also predicted alcohol dependence later in life.
3. To establish which of the premorbid predictors of alcoholism that predicted the course of alcoholism once it began (i.e. remission vs. current alcoholic drinking).
4. To identify premorbid measures that distinguished alcohol dependence *and* at the same time predicted remission to search for underlying dimensions (i.e. endophenotypes) that might account for both characteristics.

3.3 DIAGNOSTIC CONSIDERATIONS

At the initiation of the Danish Longitudinal Study on Alcoholism back in 1979, two diagnostic manuals were available for clinical and research purposes: The International Classification of Diseases (ICD-8) [66] and the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) , edited by the American Psychiatric Association [67].

In our study, we decided to use the DSM-III criteria because of their more detailed and specified description and their demarcation between alcohol abuse and dependence (see below). Another important reason is that the course specifiers (full /partial, early/sustained remission) are more systematically defined in the DSM-system when compared to the ICD-manual. Here it should be mentioned that the two diagnostic systems have facilitated a mutually productive interchange and increased their compatibility in the DSM-IV and ICD-10 editions.

In DSM-III-R, alcohol *abuse* is defined as a maladaptive pattern of alcohol use manifested by recurrent and significant adverse consequences related to the repeated use of alcohol. The criteria focus on social, legal and interpersonal problems. The criteria of alcohol *dependence* require additional presence of physiological reactions, indicated by occurrence of withdrawal symptoms and tolerance. This diagnostic distinction was used in our study because we hypothesized that alcohol dependence (but not alcohol abuse) have prognostic significance concerning remission vs. current alcoholic drinking. Both at the 30 year and 40 year follow-up examination we have utilized DSM-III R criteria for the reason of compatibility. At the 30-year follow-up, the DSM-IV had not been created.

3.4 MATERAL & METHODS

3.4.1 Original sample

The subjects in the Danish Longitudinal Study of Alcoholism were selected from a Danish cohort of children born between October 1959 and December 1961, and included 9,125 consecutive deliveries at the Maternity Department at Rigshospitalet (National University Hospital) in Copenhagen. All living cases in the cohort were examined extensively as part of a perinatal study to identify predictors of birth anomalies and motor development at age 1 year [68]. The perinatal data collection included a comprehensive set of variables obtained by midwives during the mothers' pregnancy, the delivery, at age 5 days and at age one year. The obstetrical records for the entire cohort included the identity of 8,440 fathers. In 1979, when the subjects were approximately 16 years old, the study group obtained access to the files of the Danish Psychiatric Research Register. Diagnostic information for all admissions to a Danish in- and outpatient treatment facility since 1969 are stored here [19]. In addition, we also obtained access to the files of the Municipal Alcohol Clinics in Copenhagen [69]. The 8,440 fathers were searched in these two files, and 448 of them were identified in one or both archival sources as having been diagnosed and treated for alcoholism, usually as an inpatient. Their 255 sons were selected for the high-risk (HR) group. Of these HR boys, 223 were available for the study, since 32 of them were excluded at the onset because of perinatal death (n = 9), adoption (n = 5), family immigration (n=7) and "not traceable" (n = 11). Each of the HR sons was then closely paired to another HR son according to age, mothers age, parity number, fathers socio-

economic status and marital status of the parents at birth of the subject. Data from every HR-dyad according to these 5 matching measures were averaged. These "averages" were used to select one control boy from the remaining pool of 7,992 fathers without diagnosis of alcoholism in either of the two archival sources. This matched low-risk (LR) group contained 106 individuals. Separate univariate analyses on the 5 matching measures did not show significant differences between HR and LR groups on any of them (see Table 1).

Table 1. Matching variables for selection of sample as a function of risk status (n = 329).

Variable	High risk (n = 223)	Low risk (n = 106)	p[1]	Total, n (%)
Age of subject				
Mother's age when preg. w/ subject (SD)	24.6 (6.60)	24.5 (6.45)	.94	
Marital status of mother, n (%)				
Single	90 (40)	42 (40)	.54	132 (40)
Married	79 (35)	42 (39)		121 (37)
Separated	5 (2)	3 (3)		8 (2)
Divorced	17 (8)	7 (7)		24 (7)
Widow	0 (0)	1 (1)		1 (0.3)
Married during preg.	25 (11)	11 (10)		36 (11)
Other	7 (3)	0 (0)		7 (2)
No. of Previous Pregnancies (SD)	2.1 (1.39)	2.1 (1.38)	.97	
Social class at age 1 (U.S.), n (%)			.18	
I–II	8 (4)	4 (4)		12 (4)
III	62 (34)	45 (45)		107 (32)
IV–V	113 (62)	51 (51)		164 (50)
X	2.6	2.5	.15	

1) p values are base on the χ^2 for categorical data and the Analysis of Variance for continuous variables.

The strategy of using a "half-size" control group was based on a compromise: A matched control group is necessary to verify the basic assumption that a statistical excess of alcoholism will be found among the male children of alcoholic fathers (HR group).

Daughters were not included in this prospective study because th
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started. If daughters had been included, a very large sample would have been needed to be included to achieve a reasonable number of affected (i.e. alcoholic) women in adulthood. The cost of doing this would have been prohibitive.

More detailed information of the sample selection and initial research procedures has been described elsewhere [70, 71].

3.4.2 Overview of participation in all phases of the study

For the sake of clarity, an overview of participation/non-participation rates at the three follow-up assessments will be described. As it appears from Figure 1, only 33 (24 HR and 9 LR) of the original 329 subjects never participated in any of the 18-19, 30 and 40 year follow-ups.

Conversely, 149 subjects (97 HR and 52 LR) participated in all three follow-up assessments.

The 18-19 year premorbid assessment: A total of 235 subjects (156 HR and 79 LR) completed an initial social history interview. Of these, 204 subjects (134 HR and 70 LR) completed the entire program in this assessment. We did not find any significant differences between participants and non-participants according to the initial matching variables.

The 30 year follow-up assessment: A total of 241 subjects (162 HR and 79 LR) participated in this examination keeping the original 2:1 proportion between the two risk groups. Of these 241, 192 (80%) also participated in the premorbid assessment 10 years earlier. A total of 89 subjects did not participate in the 30 year follow-up: 47 did not respond to any applications, 30 refused to participate and 12 had died.

The 40 year follow-up assessment: A total of 202 subjects (134 HR and 68 LR) participated in this follow-up. Of the 127 non-participants, 48 did not respond, 47 refused, 21 were dead, 6 had emigrated and 5 could not be located. Participation was not associated with risk status: 134 (67%) of the HR and 68 (33%) LR subjects participated in the study, reflecting that the initial 2:1 ratio of HR and LR subjects was also maintained at the 40 year follow-up.

The final number of subjects with sufficient outcome data regarding adult alcoholic drinking is 260 (183 both in 30 and 40 year follow-ups, 58 in 30 year follow-up only and 19 in 40 year follow-up

Table 2. Composition of teacher questionnaire scales.

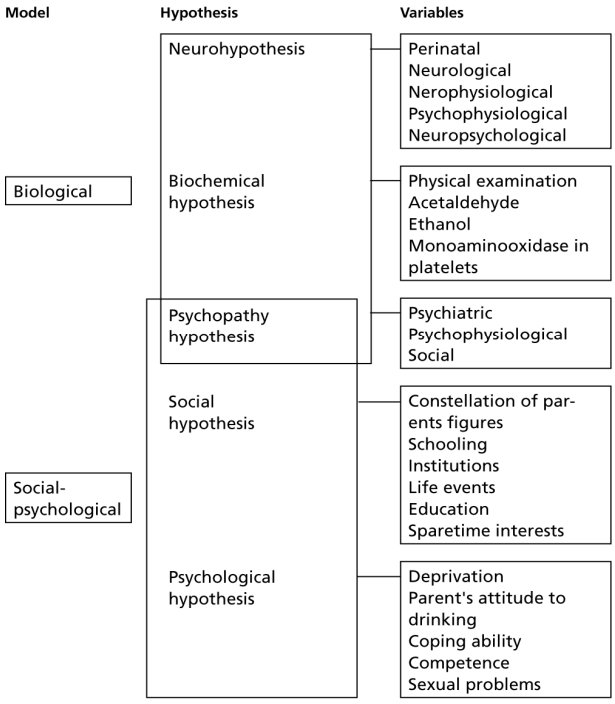
Impulsive-restless	Nervous	Violent	Independent	Withdrawn	Verbal proficiency	Math proficiency
Fidgeting	Nervous	Often in fights	Able to work independently	Daydreaming	Good vocabulary	Understands math concepts
Restless	Nervous habits (e.g. nail biting)	Aggressive	Benefits from working independently	Shy	Good reading ability	Good math ability
Confused	Anxious in unfamiliar situations		Unaffected by criticism and teasing	Not popular	Good oral expression	
Poor attention, distractable			Self-confident	Uneasy with girls		
Speaks without thinking			Self-reliant	Ineffective in group work		
Poor emotional control			Independent	Passive		
Gives up easily				Lonely		
Impulsive				Afraid of contact		
				Few friends		
Alpha coefficient						
.88	.76	.75	.76	.85	.88	.92

shown in Figure 1. This aspect is a well-known limitation factor in long-term follow-up studies, and has been described in detail in section 2.2.

3.4.3 Slection of variables

Even during the planning phase of this long-term study, the research group recognized that alcoholism is a condition with an especially complex etiology that includes both genetic/biological, psychological and social elements. In addition, we anticipated that the original selection of variables and instruments may have become obsolete/outdated in follow-up examinations decades later. Consequently, we focused on a multidisciplinary approach. Nevertheless, every effort was made to select variables representing the most solid and specific hypotheses in the field of clinical research on alcoholism in the initial phase of the longitudinal high-risk study [70].

Figure 2.



The originally selected variables and their corresponding hypotheses are listed in Figure 2.

As noted, the primary hypotheses cover a wide range of domains: Neurological, biochemical, personality-related, social and psychological models most solid and established at that time.

During the course of the longitudinal study, new hypotheses were developed (i.e. ADHD, conduct disorder), and suitable instruments and variables have successively been added in the follow-up assessments.

3.4.4 Overview of the perinatal data

The Copenhagen Perinatal Cohort 1959-61 studied approx. 9,000 consecutive pregnancies and deliveries to examine the perinatal variables' predictive power for the children's health and development [68]. The variables included social and medical health of the pregnant woman, complications during pregnancy and birth, birth weight, and the babys condition at birth, day 1 and 5, development and diet during first year of life (including age of weaning) and rating of the general physical condition at age one year. The perinatal database provided approx. 2,000 variables for analysis for each child. In connection with the present study it should be mentioned, that the extensive midwife interview did not include information of the pregnant mothers alcohol consumption. At that time, a pregnant woman's alcohol habits were considered irrelevant.

3.4.5. Overview of data from school period

Data from the subjects' school period originated from three sources: 1)The *social history interview* (see paper II) and 2) a *school teacher* questionnaire (see paper I) *,* both used in the premorbid assessment at age 18-19. 3) Also data from school physicians' records were collected.

The social history interview was conducted by a social worker and covered the following domains: living conditions, accommodation, family circumstances, major life events (at age levels up to the present), education, employment and financial circumstances. Also questions about the subjects school career were asked: Number of schools, repeating a grade, academic achievement, social aspects, relationships with teachers and peers, referral to a school psychologist.

The school teacher questionnaire was developed from a rating of school behaviour devised in another study [72], who drew on the same birth cohort. The questionnaire covered the childs intellectual, emotional and social functioning as rated by the teacher most acquainted with him (in Danish: klasselærer). Focusing on putative alcohol-related antecedents, we constructed seven *a priori* scales in order to measure dimensions of interest for development of alcoholism later in life. Each scale was subjected to an item analysis using Cronbachs alpha coefficient [73] to ensure a reasonable degree of coherence of the scale items. The seven scales were: Impulsive/restless, violent, nervous, independent, withdrawn, verbal and math proficiency. The selected scales and the alpha coefficients of the scales are shown in Table 2.

The results from the school teacher questionnaire are presented in paper I and described in detail in section 4.2.

3.4.6 Overview of premorbid assessment at age 18-19

The major aim of the first assessment was to discover premorbid measures from multiple domains that distinguished HR-sons from LR-sons. As noted previously, the study group has kept a multidisciplinary approach in the selection of variables from the very start of the longitudinal follow-up study.

The first step in this extensive assessment was the social workers visit in the subjects home who were informed about the project, which was presented as a follow-up of the original perinatal study 1959-61. The primary purpose for the visit was to motivate the subjects to participate in the assessment at the institute and to conduct a *social history interview*. The interview covered the following domains from childhood and adolescence: Living conditions, family circumstances (parental figures up to the present), 19 major stressful life events, schooling, professional training, present financial situation and hobbies.

During a whole day at the institute, the subjects were subsequent examined with the following test procedures:

Neuropsychological test program: Handedness, WAIS Vocabulary Subtest, Memory-Paired Associates, Visual Gestalts, Picture Recognition, Attention, Word Fluency, Field Dependence, Halstead Category Test, Association Test and Porteus Maze [74].

Psychological interview: Included mental health of the subject and his first-degree relatives, coping ability, competence level, self-reported criminality, drug experiences, alcohol history including first drink, first time drunk, weekly amount and preference, hangovers, level of tolerance, attitudes toward alcohol and alcoholism and parents's drinking habits. Also psychological effects of alcohol ingestion (anxiety reduction, better social ability) were asked. The interview also covered clinical signs of psychosis, affective disorder and character disorders, with special reference to impulsivity/restlessness [71]. The diagnostic criteria were in accordance with International Classification of Diseases, eighth edition (ICD-8) [66].

Medical history covering 23 diseases, *medical complaints* (12 organ-related complaints) and a *medical examination* (42 variables) conducted by the author.

Neurophysiological test program: Resting EEG, EEG + Visual Evoked Potentials and alcohol challenge test [75, 76].

3.4.7 Overview of follow-up assessment at age 30

The primary purpose of the 30 year follow-up assessment (1989-1992) was to examine which of the variables from the premorbid assessment at age 18-19 that distinguished HR and LR subjects, *also* predicted DSM-III-R criteria [67] of alcohol abuse/dependence at age 30. Data reduction and a multivariate analysis was used to identify those putative markers, in combination or in isolation, that maximized the predictive power of alcohol abuse/dependence at age 30:

First step was to identify those measures that significantly distinguished HR from LR subjects, before any problem with alcohol had developed. We assumed that this selection strategy based on the high-risk paradigm was most likely to identify measures that may play a "causal" role in the development of alcoholism. Next step was to test these HR vs. LR differences as putative markers/predictors for presence/absence of DSM-III-R alcohol abuse/dependence at age of 30. Those differences that did not predict alcoholism were then eliminated from the multivariate analyses. This two-step approach minimizes chance findings and maximizes the identification of measures that contribute, directly or indirectly, to the development of alcoholism. Also many perinatal and 18-19 year measures (incl. the electrophysiological tests) were eliminated due to insufficient variance and missing data. This "winnowing" process resulted in a total of 394 variables, that were tested for premorbid HR vs. LR differences and +/- alcohol abuse/dependence at age 30. Only items that differentiated *both* risk and an alcohol diagnosis were tested for redundancy, resulting in a final list of putative markers entered into a multiple regression containing 12 variables (see 4.4).

The assessment was organized as clinical interviews either in the subject's home or at Institute of Preventive Medicine conducted by a psychiatrist who was blind to subjects' original risk status.

We intended to use measures covering the same domains as we used in the premorbid assessment 10 years earlier: A diagnostic evaluation according to DSM-III -R criteria, an extensive psychosocial interview, Michigan Alcohol Screening Test (MAST), neuropsychological testing and Millon Clinical Multiaxial Inventory (MCMI). The diagnostic evaluation was based on the Psychiatric Diagnostic Interview, forth edition (PDI-R) originally designed to implement Feighner-criteria [77] and later modified for the DSM-III and -IV editions. The PDI is a descriptive, fully operationalized, criterion-referenced and structural diagnostic interview covering 20 basic DSM psychiatric syndromes, including alcohol abuse and dependence [78, 79].

From the Psychosocial Interview a Childhood Unhappiness Scale was created as a predictor variable. It is a retrospective summation of the subject's reported happiness/unhappiness up to age 18. Also a 32-item Alcoholism Severity Scale was constructed to evaluate the major symptoms of alcoholic drinking in the past year and over the subject's lifetime.

The following variables were used as outcome measures in the 30 year follow-up: 1) Any DSM-III-R diagnosis of alcohol abuse/dependence derived from the PDI-R interview. 2) Any DSM-III-R diagnosis made of the interviewer based on all information gathered during the interview. 3) Number of lifetime alcoholism symptoms (out of 20) based on PDI-R-symptoms, serving as a continuous index of lifetime alcoholism severity.

The collected data were supplemented by data from nationwide archival sources (see 3.4.9.).

3.4.8 Overview of follow-up assessment at age 40

The purpose of the 40 year follow-up assessment (2000-2004) was to establish which of the premorbid markers of risk and alcohol dependence *also* predicted the course of alcoholism once it began (i.e. remission vs. current dependence). And to identify premorbid measures that distinguished alcohol dependence *and* predicted remission to search for underlying dimensions that might account for both characteristics. We hypothesized that measures which distinguished risk and predicted development of alcohol use disorders in adulthood would also predict a poorer course of alcoholic drinking. We thought that these measures would constitute a group of especially powerful measures that could advance the understanding of how alcohol develops and why it is sustained [80].

The DSM-III-R criteria of alcohol use disorders include course specifiers with different categories of remission (early full, early partial, sustained full and sustained partial remission). Six months of remission following alcohol dependence is the minimum time required for early remission.

The 40 year follow-up was organized as clinical interviews (conducted by the author) in the subjects' home or at Institute of Preventive Medicine. The subjects were invited to participate by a letter that described the research procedures, their previous participation/ non-participation and information about approval from the Danish Ethical Research Committee. The interviewer administered a series of structured interviews, rating scales and questionnaires: Psychosocial Interview, Psychiatric Diagnostic Interview (PDI-IV), Millon Clinical Multiaxial Inventory (MCMI), Michigan Alcohol Screening test (MAST) and Connor's Adult ADHD Scale [100]. At the end of the session, the interviewer recorded his DSM-III-R lifetime diagnoses and a remission rating to all Alcohol Use Disorders [67]. We used DSM-III-R diagnostic criteria in order to maintain consistency with the 30 year follow-up when they were first applied.

As in the 30 year follow-up, we had access to the following nationwide registers: The Danish Psychiatric Research Register, Copenhagen Alcoholism Clinics' Register, Danish Register of Causes of Death and the Danish Central Hospital Register.

The outcome measures were DSM-III-R Alcohol Use Disorders, the lifetime Alcoholism Severity Scale and remission as defined in DSM-III-R.

3.4.9 Overview of the archival sources

Throughout the subsequent follow-up phases the study group

have obtained access to the following archival sources:

Danish Civil Registration System: The Danish Civil Registration System (in Danish: CPR-registeret) contains individual ID-numbers for all live and dead Danish inhabitants. Updated addresses and basic social indicators (i.e. civil status, occupation, inability pension etc.) are also stored in the register.

Danish Psychiatric Central Register: The Danish Psychiatric Central Register contains systematic data on admissions into psychiatric wards since 1938. As of 1969 these information have been computerized. Since 1995 information from outpatient clinics and visits to psychiatric emergency units have been included in the current data collection [19].

Copenhagen Alcohol Clinics Register: The so-called WINALCO - database contains all records (n = approx. 30,000) in the outpatient alcohol clinics in the Municipality of Copenhagen since 1954 [69].

Danish Hospital Discharge Register: Since 1976 this registry has collected basic information (including discharge diagnoses) on all hospital admissions to Danish hospitals [81]. Since 1995 the same information from emergency units and out patient clinics have been registered.

Danish Military Draft Board Register: All Danish males are required to appear before the draft board for conscription at age 18. The examination includes an IQ testing (Børge Priens Prøve), which is a reliable and valid measure of general IQ [82].

Danish Register of Causes of Death: Since 1943 information about causes of death of all Danish inhabitants have been collected and contained in this registry, maintained by the National Board of Health [83].

Primarly, we have used these nationwide registers to 1) identify updated addresses of the subjects in the follow-up phases, 2) search for current medical and psychiatric hospital-based diagnoses and 3) updated information of causes and circumstances of death. In addition, the disease-registers (in particular the Danish Psychiatric Central Register) have been valuable sources to compare the non-participant subjects vs. participating subjects regarding psychiatric illness, including Substance Use Disorders.

3.5 STATISTICAL ANALYSES

Data collected at different phases of this study were organized into ten research protocols that reflected both the temporal order of the collected data as well as the domain of interest. Each variable in every data set was identified by name and a unique number that allowed investigators to easily move from one protocol to another, merge two or more protocols, or add new protocols. A total number of 9,332 unique variables were identified and stored in a large, integrated SAS data set. *A priori* derived or secondary variables were created immediately, such as the number of life stresses endorsed at age 19 or the number of psychiatric syndromes found on the structured Psychiatric Diagnostic Interview.

The earliest analyses focused on group comparisons of high and low risk subjects on multiple variables collected from birth before any subject had developed a problem with alcohol. Typically, the Chi Square Test ($\chi^{2)}$, the Mantel-Haenszel Chi Square, or the Fisher's Exact Test was employed with categorical measures and the Analysis of Variance (ANOVA) or the General Linear Model (GLM) procedure with continuous measures. Data contained in most protocols were examined for correlations both within and across various protocols to determine associations of relevance to the first question addressed by this study: Namely, what, if any, premorbid differences distinguished low and high risk boys in their late adolescence before any had developed an Alcohol Use Disorder.

Because of the tendency for the premorbid measures to correlate with one another, logistic models were applied to identify the most independently powerful variables that predicted adult alcoholic drinking. At this phase of the investigation, small sub-studies were performed to address more specific hypotheses about antecedent predictors of alcoholism such as the effect of ADHD and different methods of defining familial alcoholism on drinking outcomes. Interest was also focused on predictors of mortality, finding that most of the premature deaths were associated with substance abuse. Finally, the study turned its attention to the prediction of remission from Alcohol Abuse and Alcohol Dependence that served as the last question addressed by the study. More complex models will be used to answer these questions. Thus far, we have used simple 2 × 2 statistical approaches to determine that premorbid risk did not predict remission from Alcohol Abuse or Alcohol Dependence. The remission rates of high-risk boys who developed an Alcohol Use Disorder did not differ from low risk boys who developed an alcohol use disorder. More complex models are to be tested to identify putative - endophenotypes of Alcoholism and its remission.

4. RESULTS

In this section, the major results from the Danish Longitudinal Study of Alcoholism is presented in a chronological order covering the life course of the subjects from pregnancy to age 40. The thesis is based on 7 selected publications among several other papers from the long-term study. They are integrated in the text to demonstrate the multidisciplinary design approach of the study.

4.1 PERINATAL RISK FACTORS (PAPER IV)

Among the premorbid variables in the longitudinal study, the perinatal data were tested 1) to examine how they were distributed in the two risk groups of subjects and 2) to analyze if they have predictive significance for the development of alcoholism later in life. *Birth weight* in the HR group was significantly reduced when compared to the LR group (HR 2955 grams vs. LR 3545 grams, $p = .05$). It was also shown that birth weight independently predicted the outcome measure of alcohol abuse/dependence at age 30 year. Birth weight accounts for 4% ($sr^2 = 0.04$) of the variance and contributes significantly and independently to the outcome prediction of alcoholism at age 30.

Time of weaning: Of the subjects who were diagnosed as alcohol dependent at age 30, 48.1% came from the group weaned from the breast before age 3 weeks, while only 19.1% of the non-alcohol dependent subjects came from the early weaning group ($p < .002$).

A standard multiple regression analysis demonstrated that early weaning contributed significantly to the prediction of the severity of alcoholism at age 30 (beta = -2.16, $p < .05$). The hypothesis about association between early weaning and alcoholism later in life is approximately 200 years old (the Trotter Hypothesis) and is confirmed in this study [84] and in another Danish study covering the entire birth cohort of approx. 9,000 individuals [85].

Vitamin K supplements in the postnatal period were generally given to preterm babies considered vulnerable to intraventricular hemorrhage and other postnatal deficits. During the original data collection in 1959 to1961 the ongoing controversy about indications of +/- vitamin K supplements was resolved and it was de-

cided to give vitamin K to all newborn babies in Danish hospitals. As described above, low birth weight and early weaning were identified as predictors for adult alcoholism, and the study group intended also to examine if vitamin K influenced the development of alcoholism in adulthood. It was found that 95% of subjects with life time alcohol dependence at age 30 had not received postnatal vitamin K treatment compared with 79% of non-alcohol dependent subjects. Just 5% of the subjects treated with postnatal vitamin K developed alcohol dependence compared to 18% of the non-vitamin K treated subjects. The difference is statistically significant (p = .02) and points in the direction that postnatal vitamin K supplement may have some protective function for future development of alcoholism [86].

Cerebellar lesions/impairments in early childhood have been associated with subsequent ADHD [87] and addiction pathophysiology in adulthood [88]. In the Danish Longitudinal Study of Alcoholism we hypothesized that risk of adult alcoholism may be associated with the functional integrity of cerebellum at birth and in the first year of life. From the extensive list of perinatal variables [68] we selected the following cerebellum-related items: Muscle tone, age of sitting without support, standing measure and walking measure. They were correlated to the outcome measure of alcohol dependence at age 30. Both muscle tone at day 5 (p = .04) and ability to walk at age 12 months (p = .0003) were scored significantly poorer among subjects with alcohol dependence at age 30 when compared to non-alcoholic subjects. These findings support the theory that early cerebellar deficits may play an important role in the development of alcoholism in adulthood [89].

4.2 SCHOOL PERIOD (PAPERS I AND II)

The course and circumstances of the subjects' *school career* is shown in Table 3.

Table 3. School career.

	HR (n = 134)	LR (n = 70)
Highest school grade attended (mean ± SD)	9.6 ± 1.3	9.8 ± 1.1
Number of schools attended (mean ± SD)[a]	3.0 ± 1.6	2.5 ± 1.3
Repeated a grade (%)[b]	20.3	5.7
Supplementary tuition (%)	31.3	24.3
Special class (%)	19.7	11.4
Referred to school psychologist (%)[c]	51.1	34.3

a) Mann-Whitney U, p = .03. b) Fisher's Exact Test, p = .007. c) Fisher's Exact Test, p = .026.

As a whole, the HR group experienced more difficulties in school when compared to the LR group, in spite of similar average number of highest grades completed (HR 9.6 vs. LR 9.8). The HR group has attended significantly more schools (mean 3 +/- 1.6) than the LR group (mean 2.5 +/- 5.7) (p = .03). Also repeating a grade was more common among the HR boys (20.3%) than the LR boys (5.7%) (p = .007). In addition, 51.1% of HR boys vs. 34.3% of LR boys had been referred to a school psychologist (p = .026). The HR boys more frequently received extra tuition and attended special classes (mostly due to reading problems, i.e. dyslexia) even if the differences between the two risk groups did not reach statistical significance.

The mean results of *behaviour and achievement in school* are shown in Table 4.

Table 4. Mean (± SD) results from teacher questionnaire scales.

	HR (n = 95)	LR (n = 49)
Impulsive-restless[a]	2.2 ± .75	1.9 ± .74
Nervous	1.9 ± .87	1.6 ± .68
Violent	1.5 ± 69	1.5 ± .71
Independent	2.7 ± .70	2.9 ± .73
Withdrawn	2.1 ± .73	2.0 ± .61
Verbal proficiency[a]	2.6 ± .97	3.0 ± .88
Math proficiency	2.4 ± .90	2.5 ± .84

a) Mann-Whitney U, p = .02.

Table 5. Parental figures during childhood.

Age, yr	Risk group	Living with both parents, %	Living with mother alone, %	Living with mother and stepfather, %
0-2	High-risk	73.1	14.9	1.5
	Control	70.0	15.7	2.9
3-5	High-risk	61.9	13.4	9.7
	Control	64.3	18.6	7.1
6-8	High-risk	53.0	15.7	17.9
	Control	55.7	22.0	8.6
9-11	High-risk	46.3	16.4	22.4
	Control	48.6	20.0	14.3
12-14	High-risk	33.6	20.1	23.1
	Control	44.3	20.0	12.9
15-17	High-risk	23.1*	18.7	23.1*
	Control	41.4*	20.0	5.7*
18-20[a]	High-risk	17.2*	16.4	18.7
	Control	37.1*	11.4	10.0

*) p < .01. a) At the time of interview, 39.1% of the high-risk group and 37.1% of the control group lived in their own accommodations.

Among the 7 a priori scales (shown in table 2) the two risk groups differed significantly on two scales: Impulsive-restless and verbal proficiency scale (p = .02) to the HR groups disadvantage. Among the items in the impulsive-restless scale, fidgeting (p < .01), restless (p < .01) and confused (p = .02) were the most pronounced deficits. In the verbal proficiency scale all 3 components (vocabulary, reading ability and oral expression) contributed equally to the significant difference between the two risk groups (p = .02)

Among the remaining 51 items in the teacher questionnaire that were not included in the 7 scales, only two distinguished the HR and LR groups: Inconsistent school work (p = .04) and poor abstracting ability (p = .02), both more pronounced in the HR group. Finally, the items in the schoolteacher questionnaire were correlated to pregnancy, birth complications, head injuries and CNS infections during childhood. No significant correlations were found.

These results indicate two sets of difficulties in the school period that impacted the development of alcoholism later in life: The impulsive/restless behaviour in the classroom points in the direction of a ADHD diagnosis (see paper VII) and specific cognitive dysfunctions [74].

Results from school physicians records: No significant differences between the two risk groups were found. However, two of the variables from the these records had predictive strength on alcohol dependence at age 30/40: "Any CNS diagnosis" (41% among alcohol dependent subjects vs. 29% among subjects without dependence, p = .07) and "any behavior disorder" (64% among alcohol de-

pendent subjects vs. 48% among subjects without dependence, p = .03).

4.3 PREMORBID ASSESSMENT AT AGE 18-19 (PAPER II)

1) *Social history interview:* The majority of subjects in both risk groups had grown up in the greater Copenhagen area. The HR boys, however, reported significantly greater number of residencies during childhood (5.0 +/- 4.0) than the LR boys (3.6 +/- 2.4) (p = .02). The distribution of parental figure during childhood and adolescence is shown in Table 5.'
2) As a consequence of the matching criterion on mothers marital status, the two risk groups are equally distributed during the first 2 years of life regarding parental figures in the home. Furthermore, it can be seen that the proportion of intact families falls steadily in both groups. However, from the age of 15 significantly fewer HR boys still lived with both parents (p < .01) and more of their mothers had remarried (p < .01). At age 18-19, 31.9% HR and 37.1% LR boys lived in their own accommodation. Only in three of the 19 major life events the HR group reported a poorer score compared to the LR group: critical economical periods (26% vs. 13%, p = .03), more parental crises (56% vs. 37%, p = .01) and more alcohol problems in the family (53% vs. 26%, p < .01). That only 53% of HR subjects reported familial alcohol problems, is mainly due to the fact that many of them had not known or could not remember their (alcoholic) biological fathers. Concerning working conditions at age 18-19, 39% were serving apprenticeships, 24% had unskilled jobs, 135 were continuing their education and 105 were unemployed. We did not find differences between the HR and LR groups in any of these categories.
3) *Psychological interview:* Of the 28 character traits and symptoms, only very few distinguished the two risk groups, reaching statistical significance. Two HR and 4 LR subjects reported hallucinations of different severity. It appeared that these hallucinatory experiences occurred during episodes of cannabis smoking. The HR group was marginally more impulsive and less antiaggressive than the LR group (p = .08), a result which is in accordance with the findings from the school teacher questionnaire (see table 4). In general, little psychopathology was found among the 204 subjects at age 18-19, and they differed only in a few respects in the two risk groups.
4) Because the assessment at age 18-19 was intended to be premorbid, it was essential to obtain information on the subjects' *drinking habits.* Table 6 shows the number of drinks (one drink equals to approx. 10 grams of ethanol) consumed in the week preceding the interview.

Table 6. Alcohol consumption in the week preceding the day of assessment, %.

Number of drinks	HR (n = 134)	LR (n = 70)
0	13.4	12.9
1-2	13.4	5.7
3-6	10.5	14.3
7-10	9.5	10.0
11-20	16.2	24.3
> 20	35.8	33.8

The two risk groups reported equal levels of alcohol consumption (average 16.8 drinks/week in HR group vs. 17.9 drinks/week in LR group). These figures may seem high according to US standards, but they do not depart considerably from the mean consumption in the general Danish population of males at the same age in 1979 [90]. We did not find any group differences regarding alcohol history (age of debut, first time drunk, motives for drinking, subjective response, hangovers, preference). Even though 36% of the HR group and 34% of the LR group reported more than 20 drinks during the preceding week, none could meet the ICD-8 or DSM-III criteria for alcoholism mainly because the subjects were virtually too young to meet the social or biological aspects of such criteria. These data indicate that the 18-19 year assessment was truly premorbid.

Except for a more common use of amphetamines among the HR boys (HR 11% vs. 3% LR, p = .06) there were no differences between HR and LR groups regarding other drug experiences or attitudes to drug taking.

5) *Neuropsychological test program:* Among the 11 neuopsychological tests (see 3.4.6), we found a significant difference between the two risk groups for 3 of them: The HR had significant poorer raw score in the WAIS Vocabulary Test compared to the LR group (p < .005), greater number of errors in the Halstead Category Test (p < .005) and in the Porteus Maze Test (p < .005). Tests of memory, attention and field dependence did not indicate differences between the two risk groups. The difficulties in control and regulation of cognition at age 18-19 may render the HR group more vulnerable to psychosocial stress and alcohol problems in the future [74].
6) *Neurophysiological tests:* As part of a session with recording of EEG and Visual Evoked Potentials (VEP), a subset of the subjects (44 HR and 28 LR) underwent an alcohol challenge test : They drank a solution of 0.5 grams ethanol/kg body weight and fruit juice during a 15 minutes period. Self reports, observer-ratings, visuomotor performance (Porteus Maze), blood alcohol concentration (BAC), EEG and VEP were measured before and 25, 55, 90 and 115 minutes after the alcohol administration.

The results showed that the HR boys' self-rating of intoxication and objective physical symptoms were significantly lower than those of the LR boys, most pronounced 25 minutes after the alcohol ingestion. We did not find significant differences between the two risk groups in the visuomotor performance or BAC [91].

The EEG after the alcohol challenge test showed an average decrease of mean alpha energy, most pronounced in the HR group, reflecting a greater reduction of anxiety and tension [92]. The VEP showed that the P 100 latency changes were significantly more lateralized among HR subjects than LR subjects [93]. A possible interpretation of this result could be a different sensitivity to ethanol in the two risk groups.

7. *Medical and neurological examination:* The medical and neurological examination did not reveal any significant differences between the two risk groups on any of the measures. In general, the vast majority of the subjects were in good health as measured at age 18-19.

Final remarks

A total of 68 variables distinguished the HR and LR groups at p < .05 level of significance in this premorbid assessment, when the subjects were 18-19 years old. In the vast majority of these comparisons, the HR subjects demonstrated the greatest degree of dysfunctions in the different tests, before alcohol drinking

had become a problem.

The study group had to wait 10 years for a follow-up examination of the subjects at age 30, when alcoholic problems were expected to have developed , to identify which of the premorbid HR-LR differences were most predictive for alcoholism.

4.4 FOLLOW-UP ASSESSMENT AT AGE 30 (PAPERS III AND IV)

Risk as a predictor of alcoholic drinking at age 30

At age 30, 41% HR subjects vs. 28% LR subjects ($p < .05$) were assigned a DSM-III-R diagnosis of either alcohol abuse or alcohol dependence. The HR sons also reported significantly more PDI-R lifetime symptoms of alcoholism when compared to LR sons (mean = 4.2 vs. 2.6; $p < .02$). As it appears from Table 7 alcohol/drug *dependence* was significantly more frequent in the HR group (29%) when compared to the LR group (15%) ($p = .02$), while alcohol/drug *abuse* was almost equally distributed in the two risk groups. Another outcome measure was the PDI-R-based lifetime Alcoholism Severity Scale that showed a significant correlation to the DSM-III-R based diagnosis of alcohol dependence ($r = .85$, $p < .0001$). Apart from alcohol, cannabis seems to be the preferred drug among the subjects in particular the HR group. According to Danish health authorities the lifetime rate of male alcoholism is estimated to be approx. 6-8% [35]. The elevated rate of alcoholism in this sample is largely due to the initial matching strategy in the two risk groups, resulting in a slightly skewed predominance to the lower end of the Danish socioeconomic spectrum.

Table 7. Substance use disorders (DSM III-R) in high and low risk subjects at age thirty, n (%).

Outcome Measure	High risk (n = 162)	Low risk (n = 79)	p[1]
Any DSM-III-R substance abuse	38 (23)	14 (17)	.31
Any DSM-III-R substance dependence	47 (29)	12 (15)	.02

1) Based on the χ^2.

A search in the Danish Psychiatric Register showed that 31.5% of the non-participants vs. 9.5% of the participants ($p< .001$) had been registered as patients to a psychiatric facility.

Psychopathology

Concerning psychopathology (other than substance use disorders) the HR and LR groups did not differ significantly in frequency of anxiety disorders, mood disorders, schizophrenia, antisocial disorder or other personality disorders. Only anxiety disorders were close to reach statistical significance (HR 13% vs. LR 5%, $p = .055$).

However, when the sample is grouped according to severity of substance use disorders (and not by risk status) some characteristic differences appear, as it can be seen in Table 8.

The lowest rate of psychopathology was found in the no abuse group. The majority of psychopathology was found in the dependence group compared with the abuse group. Most striking is the co-morbid correlation between dependence and antisocial personality disorder (ASPD), ($p = .001$).

Identification and validation of putative markers

Univariate tests used to compare the two risk groups of subjects found that 68 of the 394 measures (described in chapter 3.4.7) distinguished HR from LR subjects at $p < .05$. The HR subjects showed the greatest degree of impairment/dysfunction before drinking had become a problem as reported in the 18-19 year assessment (see 4.3).

Of these 68 variables, 27 of them also distinguished subjects with and without a DSM-III-R diagnosis of alcohol abuse/dependence. We added the PDI-R derived diagnosis of ASPD to the list of the 27 measures, because this condition was the single most powerful variable associated with the development of alcohol dependence at age 30. Altogether, these 28 measures were identified for final testing as putative markers. In Table 9 these measures are listed according to HR vs. LR comparisons on the left side and the presence vs. absence of alcohol abuse/dependence at age 30 on the right side. It can be seen that the list of measures include all study domains from birth to age 30. Apart from one of these significant risk comparisons, the HR sons showed more dysfunction/impairment than LR sons. The only exception was panic attacks that were reported more often in LR sons ($p = .006$). The same tendency was found according to drinking outcome at age 30, where the HR sons with alcohol abuse/dependence were inferior to or functioning less optimally than the subjects without abuse/dependence.

Table 8. Psychiatric diagnoses in 241 subjects at age 30 years grouped according to substance use disorders, %.

DSM-III-R diagnoses	No abuse (n = 139)	Abuse (n = 43)	Dependence (n = 59)
No diagnosis	84	72	31
Anxiety disorders	6	12	19
Mood disorders	5	14	17
Schizophrenia	0	0	7
Other axis 1 diagnosis	1	0	3
Antisocial personality disorder	1	5	44*
Other personality disorder	3	2	12

The figures are not additive, since 16 subjects have more than one diagnosis. *) $p < 0.0001$.

Final predictors of lifetime alcoholic drinking

Next step in the effort to identify final independent predictors of alcoholic drinking at age 30 was to determine those of the 28 putative markers that were most strongly associated with number of lifetime drinking problems, in particular when the co-variation or redundancy between them were eliminated. Examination of a correlation matrix with the 28 variables resulted in the elimination of 16: Seven were eliminated due to missing data, five because they were so highly correlated with a more comprehensive measure , such as individual life crises with total number of life crises and four because they were no longer independently predictive of alcohol abuse/dependence when clustered with other measures from the same domain. The final 12 variables are shown in Table 10.

They were placed in a standard multiple regression analysis (using PROC REG ,SAS) to predict the number of lifetime PDI-R alcoholism symptoms as shown in the table where the unstandardized regression coefficients (beta) intercept, the semipartial correlations (sr^2), R^2 and adjusted R^2 are presented. The R for full model was significantly different from zero ($F = 6.68$, 12/105 df, $p < .0001$). Only four of the 12 variables contributed independently to the outcome prediction of alcoholic drinking: ASPD uniquely accounted for 7% of the variance ($sr^2 = 0.07$), number of life crises accounted for 6% ($sr^2 = 0.06$), birth weight for 4% ($sr^2 = 0.04$) and ratings of childhood unhappiness for 3% of this drinking outcome measure ($sr^2 = 0.03$). Altogether, 46% of the variance (39% adjusted) in the lifetime drinking severity measure was explained by the model. Variance explained uniquely by the first seven listed predictors was 23%, while the remaining 23% reflects shared

variability. The model did not change when the 18-19 year variables for early antisocial behaviour and childhood unhappiness were substituted in the regression analysis for the 30 year measures of ASPD and childhood unhappiness. Systematic addition of all of the 28 variables did not change the model substantially.

Table 9. Measures that distinguished high- from low-risk (n = 330) and alcohol abuse/dependence from no alcohol abuse/dependence at age 30 (n = 241).

Measures	Low risk (n = 107)	High risk (n = 223)	p	No alcohol abuse/ dep. (n = 153)	Alcohol abuse/ dep. (n = 88)	p
Perinatal items						
Birthweight[a], grams	3,545	2,955	.05	3,550	2,900	.04
Socioeconomic status[a]	3.4	2.9	.007	3.3	2.5	.004
10-year school physician items						
Any CNS diagnosis[a]	24	37	.02	27	43	.06
Any behavioral disorder	44	59	.02	46	60	.06
School teacher questionnaire (1-4; higher = worse)						
Oral expression	1.9	2.3	.06	2.1	2.5	.02
Vocabulary	2.0	2.5	.02	2.2	2.6	.07
Task concentration	2.1	2.4	.07	2.1	2.6	.005
Daydreaming	1.6	2.1	.01	1.7	2.3	.02
Restlessness	1.8	2.3	.01	1.8	2.4	.008
19-20-year physical examination						
Migraine[a], %	1.4	8.2	.05	3	10	.07
Weight[a], kg	70.9	68.5	.07	70.2	67.3	.05
19-20 year neuropsychological examination						
Porteus mazes, no. wrong att.	0.7	1.2	.006	0.7	1.2	.006
19-20 year psychological interview						
Amphetamine use	3	10	.06	3	15	.002
Difficulty sitting still[a]	36	49	.08	39	66	.01
Panic attack	17	5.2	.006	5	15	.01
Father, psychiatric treatment	40	58	.02	26	49	.02
Mother, psychiatric problems[a]	46	58	.04	28	45	.07
19-20 year social worker interview						
Special class, ever	80	85	.09	13	32	.02
School psychologist[a]	34	51	.02	42	65	.02
Juveinile autorities	14	22	.07	33	67	.04
Alcohol problems in family	23	51	.0001	36	51	.03
Number life crises (out of 20)[a]	4.3	5.3	.03	4.1	6.1	.001
30-year psychosocial interview						
Mother in psychiatric reg, %	10	23	.005	13	27	.006
Childhood unhappiness[a] (mean) (1-4; higher = worse)	2.0	2.1	.07	2.0	2.3	.0001
Childhood deviance (mean) (1-3; higher = worse)	1.2	1.3	.0001	1.2	1.4	.0001
Number of medical conditions	1.0	1.6	.001	1.2	1.6	.01
Number of familial syndromes	1.1	1.2	.0001	1.6	2.1	.05

a) Variables were entered into the multiple regression. Not shown are risk and antisocial personality disorder that were also included in multiple regression.

It is interesting that risk status did not emerge as a significant predictor of alcoholic drinking at age 30 in this analysis. A two-way ANOVA was used to examine any interaction between risk and the seven strongest variables, and showed that six of them did not interact significantly with risk, the predictor variable and drinking outcome. Only the variable "difficulty in sitting still" as reported at age 18-19 did result in a significant interaction ($F = 5.56$, 1 df, $p < .02$).

Other findings

The EEG after alcohol administration at the premorbid assessment showed a decrease of mean alpha energy, most pronounced in the HR group [75]. This finding did not relate to alcohol dependence at age 30. However, a smaller EEG alpha frequency response to alcohol at age 18-19 was correlated to alcohol dependence 10 years later [94].

Among the HR vs. LR differences in the neuropsychological test battery at age 18-19, only two variables were associated with alcohol dependence at age 30: Word Fluency ($p = .007$) and no. of errors in the Porteus Maze Test ($p = .02$). All other neuropsychological tests from the premorbid assessment at age 18-19 did not possess predictive power.

Similarly, the HR-LR differences in the clinical response to alcohol challenge at age 18-19 were not associated with alcoholic drinking at age 30.

Table 10. Results of standard multiple regression predicting the numbers of PDI lifetime alcoholism symptoms endorsed at age 30.

Variables	Epoch	β	sr^2 (unique)
Birthweight[a]	Perinatal	-0.765**	.04
Number of life crises[a]	20-year	0.396**	.06
Antisocial personality disorder[a]	30-year	6.222**	.07
Childhood unhappiness rating[a]	30-year	1.838*	.03
Weight at 20 years[a]	20-year	-0.064	.01
Difficulty sitting still (school)[a]	20-year	1.12	.01
CNS disorder (physician records-10 yr)[a]	10-year	0.955	.01
SES at 1 year of age	Perinatal	-0.172	.003
Saw school psychologist	20-year	0.241	.000
Migraine pressent (20-yr medical exam)	20-year	0.575	.000
Mother in psychriatric register	30-year	0.205	.000
Risk status	20-year	-0.329	.001
Intercept		-2.885	
$R^2 = 0.46$, $F = 6.68$; 12/105 df; $p < .0001$			
Adjusted $R^2 = 0.39$			

Unique variability = 0.23; Shared variability = 0.23. R^2 = total percent og variance ine outcome measure (no. PDI alcoholism symptoms endorsed at age 30) that is explained by this regression analysis with these 12 variables. The model is significant at $p < .0001$. sr^2 = percent of variance in outcome measure (no. PDI alcoholism symptoms endorsed at age 30) that is explained uniquely by each variable (e.g., 4% of the variance in the number of alcohol symptoms endorsed at age 30 is explained by birthweight). a) These items were used in the ANOVA to test for possible interactions between risk and these items. *) $p < .05$. **) $p < .001$.

4.5 FOLLOW-UP ASSESSMENT AT AGE 40 (PAPERS V, VI AND VII)

Prediction of mortality (paper V)

The main question addressed in this study was: Does genetic vulnerability (defined by paternal alcoholism) predict premature mortality at age 40 regardless of drinking history ? And to what extent is premature death correlated to selected premorbid factors like perinatal factors and psychiatric diagnoses ? Due to the expected small number of death cases at age 40, we limited our search for predictive factors to data extracted from the following archival sources: Danish Causes of Death Register, Danish Central Psychiatric Register, Municipal Alcohol Clinics' Register and the perinatal data file in the study (see 3.4.9).

The search in the Danish Causes of Death Register identified *21 deceased subjects.* The average age at death was 31 years. Eleven died in their 20s, eight in their 30s and two at age 41.The

mortality rate for the entire sample was 6.38% (21 of 329 subjects). When compared to the age- and gender-corrected mortality rate for Danish males between age 18 and 40 (2.17%), the Standardized Mortality Rate (SMR) in our sample is significantly increased (95% CI 0 1.68-4.20, p < .003). This indicates that the death rate in our sample was almost three times greater than found for the Danish reference group.

Table 11. Descriptive findings for the 21 subjects who died by age forty years.

Subjects			Death certificate			Danish Psychiatric Register	
risk status	20-year follow-up	30-year follow-up	death age	cause of death	other Information	no. of admissions	ICD diagnosis
High	No	No	21	Accident	Alc. + drug abuse	1	Delirium
High	Yes	No	30	Suicide	Alc. abuse	4	Borderline
High	Yes	No	28	Cancer	None	0	–
High	Yes	No	26	Accident	None	0	–
High	Yes	No	26	Accident	Epilepsy, alc. abuse	2	Delirium
High	No	No	24	Accident	Alc. + drug abuse	3	ASPD
High	Yes	No	29	Suicide	Alc. abuse, schizophrenia	3	Schizophrenia
High	No	No	36	Unknown	Drug abuse, schizophrenia	2	Schizophrenia
High	Yes	No	39	Accident	IV drug abuse	2	Alcoholism
High	Yes	No	33	Accident	Alc. + drug abuse	0	–
High	Yes	Yes	33	Accident	Drug abuse	0	–
High	No	No	39	Accident	IV drug abuse	2	Schizophrenia
High	No	No	35	Accident	IV drug abuse	1	Paranoia
High	No	No	33	Accident	Alc.+ drug abuse	5	Psychosis
High	No	No	41	Accident	Alc. + drug abuse	10	Schizophrenia
Low	Yes	No	25	Accident	None	0	–
Low	No	No	27	Suicide	Drug abuse, criminality	9	Opiate abuse, ASPD
Low	Yes	No	25	Accident? Suicide?	Alc. abuse	0	–
Low	Yes	No	26	Suicide	Drug abuse	5	Drug abuse
Low	No	No	29	Accident	None	0	–
Low	Yes	Yes	41	Cancer	None	0	–

Table 11 illustrates risk status, previous participation in the study, data from death certificates and from the files of the Danish Psychiatric Register for the 21 deceased subjects. The distribution of the causes of death found among the 21 subjects is similar to the distribution of causes of death in the Danish male population of males at age 40 [95]: Accidents accounted for 66%, suicides for 19%, cancers for 10% and unknown causes for 5%. The 14 cases of accidents included 5 intoxications, 3 traffic accidents, 1 drowning, one postconvulsive accident, one fall, 1 electrical accident and 2 unclear descriptions of the accident. All 4 subjects who had suicided, had been admitted several times to a psychiatric ward due to drug abuse. Other co-morbid diagnoses were borderline personality disorder, schizophrenia, paranoid psychosis and antisocial personality disorder (ASPD). Altogether, 16 of the 21 (76%) deceased subjects carried a diagnosis of substance use disorders. These results reflect severe psychiatric morbidity at a relatively young age for those who later died prematurely. It should be added that the two cases of cancer death had no psychiatric history.

The next analysis examined the relationship between paternal risk and premature death. We did not find a significant difference between the HR group (n = 15, 6.6%) and the LR group (n = 6, 5.6%), (χ^2 0 .15, d.f. 0 1, p < .70), indicating that genetic vulnerability did not contribute independently to premature death.

We also examined differences between dead subjects (n = 21) and survivors (n = 308) with respect to the premorbid archival data obtained from the perinatal period, the Danish Psychiatric Register and the Municipal Alcohol Clinics' files. There were no significant differences between the alive and dead subjects in eight of the nine perinatal summary scales used in the study. Only on the scale of physical examination at age 1 year, the deceased subjects had a poorer score than the survivors (p .03).

Most striking is that 66.7% of the deceased subjects vs. 12.0% of the survivors had been hospitalized in a Danish psychiatric facility (p < .001). In addition, the mean number of separate admissions was significantly higher among the deceased subjects (4.47 vs. 0.45, p .0001). Also the number of different psychiatric ICD-8 diagnoses was higher in the deceased group (2.00) than in the survival group (0.22), (p < .0001). Similar results were found in the files of the Municipal Clinics.

Finally, we performed a logistic regression analysis with death by age 40 as outcome variable.

In Table 12 the predictive role of risk status and the five archival variables (described above) that were associated with premature death served as independent predictors was examined. As it can be seen, two archival variables predicted death by age 40: Psychiatric hospitalization increased the risk of dying prematurely 5.3 times, while deviant physical examination at age 1 year increased the risk for early death by 8 percent. Tests for possible interactions between risk and the significant predictors did not indicate any interaction in predicting premature death.

Table 12. Logistic regression analysis of mortality as a function of risk status, psychiatric register variables, and a perinatal summary scale.

Variables	Parameter Estimate	χ^2	Odds ratio	95% confidence interval for odds ratios lower	upper
Risk status	0.03	0.003	1.03	0.33	3.29
Presence in psych. registry	1.68	5.67**	5.34	1.34	21.29
No. of Psych admissions	0.02	0.11	1.03	0.86	1.23
No. of Psych diagnoses	0.33	1.09	1.39	0.75	2.56
Presence in alcohol files	1.40	1.80	4.07	0.52	31.69
1-year physical exam	0.08	5.69**	1.09[1]	1.015	1.17

**) p < .02. 1) Indicates that every unit increment in the scale (00-39) increases the risk of death at age 40 by 8%, other variables being equal.

Development, clinical course and remission of alcoholic drinking (paper VI)

Socio-demographic characteristics

Education: Nine percent of the sample had finished high school, 49% the 10th class, 29% the 9th class and 13% less than 9th class. Seven percent received some university training, 16% achieved a BA (in Danish: mellemuddannelse), 41% were classified as skilled workers and the remaining 35% were semi-skilled or unskilled

workers. Concerning marital status, 44% were currently married, 25% co-habiting, 13% were separated/divorced/widowed and 18% had never married. Eighty-three percent was currently employed at time of the interview. These socio-demographic characteristics of the 40 year follow-up sample closely resembled the general population of Danish men at same age in the year 2000, when the interviews took place [95].

Paternal risk and lifetime prevalence of alcohol abuse and dependence

In Table 13 the effect of paternal risk on several DSM-III-R diagnoses of alcohol use disorders is shown.

The HR group was significantly more likely to develop alcohol *dependence* (31%) than the LR group (16%), (p = .03). However, paternal risk did not predict alcohol *abuse* (HR 17% vs. LR 15%). The total mean lifetime MAST score was 8.5 (SD = 12.67) in the HR group compared to 4.4 (SD = 10.00) in LR group (p = .02). Twenty-two percent of HR subjects vs. 12% of LR subjects met the MAST-criteria of alcoholism with a cut-off score > 5 (p = .04).

Table 13. DSM-III-R lifetime alcoholism disorder in high and low risk subjects at age forty, n (%) (n = 202).

Outcome Measure	High Risk (n = 134)	Low Risk (n = 68)	p[1]
Alcohol abuse/dependence	64 (48)	21 (31)	.02
Alcohol abuse	23 (17)	10 (15)	.65
Alcohol dependence:	41 (31)	11 (16)	.03

1) Based on separate χ^2 analyses for each disorder.

The search in the two national archival sources confirmed these results: Of the 202 interviewed subjects, 10% HR vs. 3% LR were found in one or both registers. When the entire original sample was searched in the registers, 12% HR vs. 5% LR subjects (p = .04) were found with a diagnosis of alcoholism.

Table 14 shows remission vs. non-remission of alcohol use disorders by paternal risk status at age 40. Of the 33 subjects with alcohol *abuse,* only 4 subjects reported receiving any treatment for an alcohol-related problem. Of the 52 alcohol *dependent* subjects, 32 (62%) had received treatment. Eighteen of the 22 (82%) *non remitted* alcohol-dependent subjects reported having some kind of treatment, while 14 of 30 (47%) *remitted* alcohol-dependent subjects reported treatment. The difference is significant (χ^2 = 6.63, df = 1, p < .01). The mean duration of remission from alcohol dependence was 11.1 year (SD = 7.47) in the HR remitted group and 11.3 years (DS = 5.01) in the LR remitted group (p = .94, range = 0.5-21 years).

These results are in accordance with US studies of admitted alcohol-dependent patients [80]. It is well-known that severely ill alcohol patients need repeated detoxifications and treatment episodes.

Are premorbid predictors of alcohol dependence and of remission at age 40 the same?

The study group asked whether the 109 premorbid measures found to predict alcohol dependence also predicted remission. Only 18 of them also predicted remission. A factor analysis identified two underlying premorbid dimensions that accounted for the failure to remit from alcohol dependence: Poorer intellectual efficiency and increased behavioural deregulation prior to the onset of alcoholic drinking [96]. These results suggest that the diagnosis of alcoholism may be divided in a benign and a malignant subtype, each with separate characteristic lifetime course (see section 5).

Table 14. Remission from DSM-III-R alcohol disorders at age forty by risk status.

Drinking outcome	High risk, n (%)	Low risk, n (%)	p[1]
Alcohol abuse/dependence (n=85)			
Active[2]	20 (31)	7 (33)	.86
Remisssion[3]	44 (69)	14 (67)	
Alcohol abuse (n = 33)			
Active[2]	2 (9)	2 (20)	.36
Remission[3]	21 (91)	8 (80)	
Alcohol dependence (n = 52)			
Active[2]	18 (44)	5 (45)	.93
Remission[3]	23 (56)	6 (55)	
Mean duration of remission from alcohol dependence (yrs)[4]	10.8 (7.49)	11.3 (5.00)	.86

1) Based on the χ^2. 2) Active = symptoms of the alcohol use disorder were present in the previous 6 months. 3) Remission = no significant impairment due to drinking in the past 6 months (does not require abstinence). 4) Duration estimate is based on information from the PDI-IV and was only available for the alcohol dependent subjects.

Childhood ADHD and conduct disorder as predictors of alcoholism at age 40 (paper VII)

Even in their teenage-years, the HR boys were rated significant more restless and impulsive by their school teachers when compared to the LR boys (see paper I). During the subsequent decades the concept of ADHD was clarified both in the DSM- and ICD-diagnostic systems. An increasing amount of scientific evidence has shown that the development of alcoholic drinking often is preceded by both conduct disorder (CD) and ADHD in childhood [97, 98].

In the present study, we used three premorbid predictors: risk status, childhood ADHD and childhood CD and two outcome measures: the DSM-III -R categorical diagnoses of alcohol dependence vs. alcohol abuse and the lifetime alcoholism severity scale (see 3.4.7). The correlation between the categorical diagnosis of alcohol dependence and the continuous lifetime alcoholism severity scale score was r = .85, p < .0001 (paper IV).

The Childhood ADHD Scale was based on the schoolteacher questionnaire (paper I). The 85 items from the questionnaire were first reviewed by a child psychologist [99] who selected 22 items (from the 85) that were consistent with the DSM-II-R criteria for ADHD. These items were given to four child psychiatrists at KUMC. They were asked to rate each item on a scale from 1 to 5 (least to most characteristic for ADHD). This procedure resulted in 12 consensually agreed-on items with a Cronbach's alpha coefficient = .92. The Childhood ADHD Scale correlated significantly with the Conners Adult ADHD Rating Scale [100] completed by the subjects at age 40.

The Childhood CD Scale was based on the social interview at age 18-19 (paper II). We selected items reflecting antisocial activities consistent with DSM-III-R criteria for Conduct Disorder. The CD-items showed adequate internal consistency (Cronbach's alpha = .69) and they correlated significantly with the DSM-III -R diagnosis of adult ASPD derived from the PDI-R interview (r = .46, p < .0001). The Childhood CD Scale also correlated significantly with the Childhood ADHD Scale (r = .36, p < 0001).

Table 15. Predictive relationships between risk, childhood ADHD and childhood conduct disorder on lifetime alcoholism severity and adult alcohol dependence and at age 30 and/or 40 years (n = 110).

Predictors	Alcoholism severity. mean (SD)	p[a]	No alc. depend. % or mean (SD)	Alcohol depend. % or mean (SD)	p[a]
Risk[b]					
High	4.4 (4.38)	.20	74%	26%	.25
Low	3.3 (3.61)		84%	16%	
ADHD Scale[c]					
Continuous (X; SD): (Range = 12-48)			25.8 (9.4)	32.3 (10.1)	.003*
Above median	5.3 (4.53)	.0001*	68%	32%	.01*
Below median	2.5 (2.82)		88%	12%	
Conduct disorder scale[d]					
Continuous (X; SD) (Range=0-13)			3.9 (2.6)	6.9 (3.1)	.0001*
Above median	6.1 (4.70)	.0001*	58%	42%	.0001*
Below median	2.5 (2.81)		91%	9%	
Alcoholism severity scale[e] (range = 00-26) (X; SD)			2.1 (1.65)	10.5 (2.99)	.0001*

*) Indicates statistical significance. a) p values based upon the GLM procedure for continuous measures and the χ^2 test for categorical measures. (SAS v. 9.1).b) High risk defined as treated alcoholism in the biological father. c) Childhood ADHD derived from school teacher's questionnaire. d) Childhood conduct disorder scale derived from Interview at age 19/20. e) Alcoholism severity scale derived from the PDI alcoholism module.

Childhood predictors

As it can be seen in Table 15, both the childhood ADHD Scale and the Childhood Conduct Disorder Scale were strongly associated with the two outcome drinking measures (DSM-III-R alcohol abuse vs. dependence and lifetime Alcoholism Severity Scale) at ages 30 and 40 ($p < .0001$). Subjects above the median on the school teacher-based childhood ADHD scale reported twice as many lifetime alcoholism symptoms as adults than subjects below the median. The effect was even more pronounced for the teen Conduct Disorder Scale where subjects above the median reported significantly more lifetime alcoholism symptoms in adulthood than subjects below the median.

Combination of paternal risk and the childhood predictors

A standard multiple regression analysis was used to examine the relative strength of the relationships between paternal risk, the premorbid ADHD and CD scales on lifetime alcoholism severity. The results from these analyses are shown in Table 16.

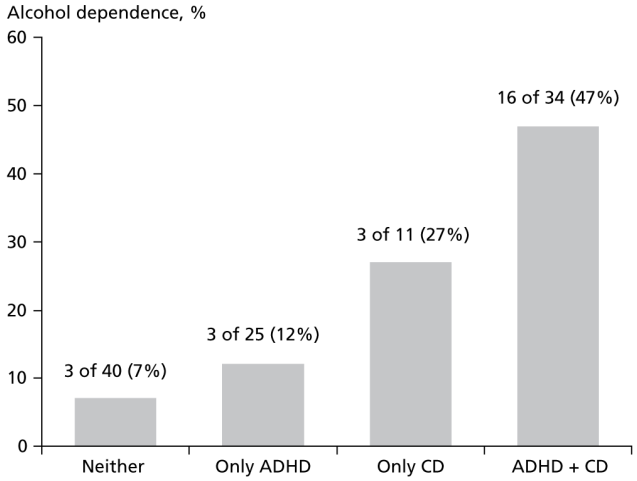
Table 16. Correlations and standard multiple regression of childhood ADHD characteristics and conduct disorder characteristics on development of later adult alcoholism severity controlling for risk status (n = 110).

	Risk status[a]	Childhood ADHD[b]	Conduct disorder[c]	Adult alcoholism severity[d]	B	sr^2 (unique)
Risk status	–	.18	.08	.12	0.45	.002
Childhood ADHD		–	.37****	.35****	1.77*	.04
Conduct disorder		–	–	.43****	2.88***	.10
Intercept = -3.53						
R^2 = .23****						
Adjusted R^2 = .21						
Unique variability = .142						
Shared variability = .088						

a) High Risk (son of alcoholic father) vs. Low Risk (son of non–alcoholic father). b) High vs. Low Scores on Childhood ADHD Scale (Median Split). c) High vs. Low Scores on Conduct Disorder Scale (Median Split). d) Represented by Number of Alcoholism Symptoms Endorsed on the PDI Alcoholism Module. (0–20). *) $p < .05$. ***) $p < .001$. ****) $p < .0001$.

The R^2 of .23 for both childhood predictors was highly significant ($p < .0001$) indicating that the model explained 23% of the variance. Childhood ADHD uniquely accounted for 4% (sr^2) of the explained variance, while childhood CD accounted for 10% of the variance. The shared variance was 9%. The intercorrelations shown in Table 16 indicate that the childhood ADHD and CD scales were significantly associated with each other, despite the fact that they were derived from very different sources at different times in the subjects' lives. The results of the multiple regression are shown graphically in Figure 3.

Figure 3. Relative risk for 30/40 year alcohol dependence as a function of attention-deficit /hyperactivity disorder (ADHD) and conduct disorder (CD).



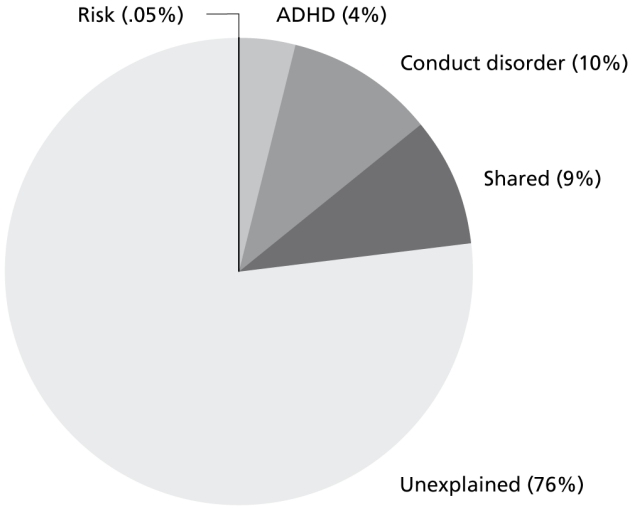
ADHD high vs. ADHD low; median split.
Cond dis. (CD) high vs. low; median split.

Cond dis. relative risk[a] = 3.6; CI = 0.8, 15.5
ADHD relative risk[a] = 1.6; CI = 0.3, 7.3
Both relative risk[a] = 6.3; CI = 2.0, 19.7

a) The relative risk estimates use the low on both measures (neither) as a reference group.

The relative risk of developing alcohol dependence in adulthood is shown in Figure 4, where the group of subjects with a score on the ADHD and CD scales below the median are used as the reference group. It appears that subjects with higher scores on the childhood ADHD scale were 1.6 times (CI: 0.3-7.3) more likely to develop alcohol dependence than those subjects with a lower score in developing alcohol dependence. A score above the median on the CD scale showed a relative risk of 3.6 (CI: 0.8-5.5). Subjects with high scores on both childhood scales obtained the relative risk of developing alcohol dependence to 6.3 CI: 2.0-19.7) indicating that they were 6 times more likely to develop alcohol dependence later in life than subjects with scores below the median on both premorbid scales.

Figure 4.



Total percent explained variance = 23%
Model: $F = 10.77$; $p < .0001$; $R^2 = .23$
Risk: $t = 0.6$; $p < .53$; $sr^2 = .005$
ADHD: $t = 2.3$; $p < .02$; $sr^2 = .04$
Conduct disorder: $t = 3.8$; $p = .0002$; $sr^2 = .10$

5. DISCUSSION

The results from twin- and adoption studies (see 1.3. and 1.4.) have demonstrated that a considerable genetic component influences the development of alcoholism besides psychological and social risk factors. As a consequence of a broad spectrum of potential etiological risk factors, we realized that the premorbid data collection in our study should be multidisciplinary in nature (illustrated in Figure 1). This strategy is often criticized as a "shotgun approach", with the statistical risk of chance findings (type I errors) due to the considerable number of variables examined. Nevertheless, the strength of our findings lies in the extent to which they support or generate hypotheses regarding the complex etiology and pathogenesis of alcoholism later in life.

The majority of clinical/etiological alcohol research is based on retrospective/cross-sectional study designs comparing alcoholic and non-alcoholic individuals. Such results cannot easily be interpreted in an etiological context, because they typically reflect a combination of antecedent, consequential or epiphenomenological factors. This is the main argument for conducting prospective long-term studies starting before the effect consuming alcohol exerts any effect.

Considering the fact that the prevalence of alcoholism is approx. 7-10% in the general male population, an impracticably large number of subjects is needed to be included in the study to obtain a sufficient outcome number of affected subjects. The established fact that biological sons of alcoholics represent a group at a well-defined increased risk (20-25%) for becoming alcoholics themselves makes them suitable for a prospective follow-up study. As a consequence, this high-risk design requires a much more limited number of subjects to be followed up over the years to ensure a sufficient number of alcoholic subjects, making the longitudinal study much more focused and less expensive to conduct.

The *limitations* , especially the problem with attrition in the longitudinal study design, are described in chapter 2.2.

Also the excess of premature mortality rate in the sample (described in paper V) have contributed to the attrition rate found at age 40. The relatively high number of dead subjects with severe psychopathology at a young age probably explains the low rate of schizophrenic/psychotic subjects identified in the follow-up examinations.

In spite of these attrition-problems, the main results from this longitudinal study remain substantial and statistically reliable.

In the 40 year follow-up, we decided to apply DSM-III-R criteria like we did in the 30 year follow-up for comparison reasons, in spite of the edition of DSM-IV that was published between the two assessments. Another example of these problems is the use of CT-scans. It would have been obvious to include CT scans as a weighty measurement in the premorbid assessment at age 20. However, it was not included in the battery for that simple reason that CT scanners were not yet introduced in Danish hospitals at that time.

The rapid development of genetic measurements during the past decade inspires the study group to include them in a planned follow-up examination, when the subjects reach the age of 50. At the premorbid assessment (1979-82), the Danish Research Council did not allow us to collect and store blood samples for future research purposes, unless we could specify the use of it. Nowadays, this restrictive attitude has been replaced by a more tolerant strategy, primary due to the promising aspects of contemporary genetic research.

In the case of alcoholism, etiology and pathogenesis is complex, undoubtedly with a complicated interplay of biological, psychological and social factors involved. Therefore, it has been important for us to keep a multidisciplinary and eclectic approach in the selection of variables throughout the years [70]. A too narrow selection of variables would have limited the conclusions of this study.

Finally, the *economic aspect* and staff problems in long-term clinical research should be mentioned. It is an old experience that such studies have special difficulties in getting premorbid assessments funded opposed to i.e. cross-sectional comparisons of patients vs. healthy controls, pharmaceutical trials or specific genetic association studies. Our study has been funded alternately from Danish and American sources throughout the decades, and it has often been a challenge to motivate the financial supporters on the necessity of the initiation before illness occurs and carrying through of a high risk study covering several decades. In addition, clinical research on alcoholism seems to have lowest priority in a funding context among the spectrum of other severe and chronic illness in society.

Regarding *staff recruitment* in the study, it has been important to develop and maintain a high qualified and consistent working milieu during the three waves of examinations. For historical reasons the Danish-American collaboration has demonstrated its tenacity since the initiation of the adoption studies on alcoholism in the 70'ies. Despite the geographically great distance between Copenhagen and Kansas City, we have succeeded in keeping the close collaboration on the study with both old and new staff members. The 40 year follow-up assessments focus on diagnostic DSM-issues (i.e. co-morbidity) required an experienced and clinically trained psychiatrist (the author) as interviewer to ensure a reliable and valid diagnostic judgement of the subjects.

The results from the *perinatal period* point to both specific and unspecific issues: In general, the HR group demonstrated more perinatal abnormalities than the LR group (see paper IV). Nevertheless, some of the specific perinatal variables independently had considerable predictive power for alcoholism in adulthood

(low birth weight, earlier weaning, poorer cerebellar function, lacking supplement of Vitamin K), while risk status (HR vs. LR) did not show the same degree of predictive power. Unfortunately, the original midwife records did not include the pregnant mothers alcohol habits, indicating that this important aspect cannot be integrated in the interpretation of the results. During the follow-ups at age 30 and 40, the Psychosocial Interview included questions about mothers alcohol pattern according to the subjects's memory.

Data from the subjects' *school period* (paper I and II) are interesting in a longitudinal and predictive context. Even if ADHD did not exist as a diagnostic entity at that time, we constructed a scale for restlessness/impulsivity as a potential predictor of alcohol problems decades later. It was inspired by results from the previous adoption studies, indicating that adopted-away sons of alcoholics were more hyperactive, disobedient and truant in childhood than matched controls [101]. Already, at that time it was proposed that hyperactivity in childhood may predispose to alcoholism. The predictive power of these premorbid findings for alcoholism at age 40 is presented in paper VII.

The results also indicate that the HR group as a whole reported considerable cognitive difficulties in school, in particular poor attention and verbal proficiency. It was in accordance with the neuropsychological findings at the premorbid assessment at age 18-19, where the HR boys had a lower verbal IQ in the WAIS battery [74]. Also the relatively poorer IQ score among the HR boys at the military draft confirms the main result of a poorer cognitive functioning as a potential predictive factor for alcoholism later in life. We also found that poor premorbid cognitive functioning could be decisive for a "malignant" course, i.e. a continuous alcoholic drinking pattern without clinical signs of remission.

The results from the extensive *premorbid assessment at age 18-19* (paper II) showed a considerable number of HR vs. LR differences. Their origin represent a broad spectrum of disciplines: Social, psychopathological and alcohol/drug-related domains (paper II), neuropsychological tests [74], and psychophysiological variables [93] and finally the measures of the effect of the alcohol challenge test [75, 76]. As a whole, the HR boys reported much more disrupted conditions in the family and in school which may reflect more instability in the family, presumably due to the fathers alcoholism. The premorbid neuropsychological deficits among the HR boys are in accordance with the results of behaviour in school mentioned above. Our findings have been confirmed by other study groups [102-105]. It suggests that the cognitive deficits found in alcoholic individuals also characterize HR adolescents before an alcoholic drinking pattern develops. The background of such deficits reflects a complex interaction of genetic, developmental and familial factors. Probably, these cognitive deficits may relate to the accumulation of ADHD-problems among the HR boys as reported by their school teachers (see paper I). Inspired by the findings, we hypothesized that poor verbal ability and poor impulse control may play a significant predictive role for development of alcoholism later in life.

The 18-19 year assessment was intended to be premorbid, that is none of the subjects met criteria of alcohol abuse/dependence. As described, we did not find any differences regarding present or past alcohol consumption, hangovers, level of tolerance, age of debut, subjective reactions etc. between the two risk groups. Their premorbid consumption did not differ from normative data on the general Danish male population of that age. As it appears from table 6, the present consumption was relatively high in both risk groups (36% HR and 34% LR subjects reported over 20 drinks in the preceding week), but none met the DSM-III-R criteria for alcoholism, mainly because they were too young to meet the social and medical consequential criteria (suspension of driving licence, divorce etc.). These findings indicate that abnormalities/deficits found in this assessment were not consequences of alcoholic drinking. We did not find any marked group differences for drug experiences, except for a marginal excess of amphetamine taking in the HR group. This result is suggestive, when seen in the light of the fact that CNS-stimulant drugs are effective in the treatment of ADHD, which *per se* is linked to subsequent alcoholism (see paper VII).

The results from the measurements of subjective and objective response during the alcohol challenge test (see 4.3.) showed lesser subjective and objective reactions among the HR boys than the LR boys. This is in accordance with the findings from the San Diego Prospective Study of Alcoholism [59]. They found a lesser sensitivity to ingested alcohol among the family-positive prealcoholic subjects compared to family-negative subjects, and hypothesized that this characteristic was a strong predictor for future development of alcoholism. It is obvious that a premorbid high level of tolerance to alcohol is a necessary facilitation for an alcoholic course.

Also the greater increase in slow alpha waves in the resting EEG [75] and lateralized differences in P100 latencies in the visual evoked potentials [93] among the HR boys after the alcohol challenge pointed in the direction of putative neurophysiological predictors of alcoholism later in life.

The primary aim of the *follow-up assessment at age 30* (paper III) was to analyze which of the premorbid HR-LR differences identified at the 18-19 year assessment also predicted lifetime drinking problems at age 30. The data reduction strategy (see 3.4.6) found that 68 of the 394 premorbid variables distinguished the HR and LR group before any of them had developed an alcoholic drinking pattern. Of these 68 variables, 28 (41%) were also associated with DSM-III-R alcohol abuse/dependence at age 30. To search for the most powerful predictors of alcoholism, 12 of the 28 variables were entered into a multiple regression analysis. We found that four of them were independently associated with alcoholic drinking at age 30: Low birth weight, number of life crisis during childhood, ratings of childhood unhappiness and antisocial personality disorder. The regression model explained 46% of the drinking outcome variance. Paternal risk by itself did not any longer contribute independently to the prediction of the sons alcoholic drinking. In general, these findings provide broad support for models emphasizing the cumulative effect over time of internal and external variables in biologically vulnerable individuals.

In particular, emotional and behavioural deregulation in childhood seem to be potent risk factors for male alcoholism, even more powerful than genetic influence. The results suggest that extreme forms of this deregulation (CD and ASPD) are sufficient themselves to develop alcoholism in males, especially when alcoholism unfolds in the context of a deviant environment (i.e. multiple life crises). Another point in this connection is the fact that "narrow"/specific premorbid factors seem to fail as predictors of alcoholism in adulthood. In contrast, broadly encompassing measures seem to be among the strongest predictors of alcoholism reflecting multiple interacting genetic and environmental influences with different effects at different periods in the individuals life.

The follow-up assessment at age 40 (papers V, VI and VI) in-

cludes analyses of mortality, remission and ADHD/CD's predictive roles in the development of adult alcoholism.

Concerning *mortality*, we identified 21 deceased subjects at an average age of 31 years. We found an significantly increased Standardized Mortality Rate compared to Danish age- and gender corrected mortality rate, indicating that the death rate in our sample was almost three times greater than found in the Danish reference group. Causes of death among the 21 dead subjects were similar to the distribution in the Danish male population at age 40. A search in the Danish Psychiatric Central Register disclosed an overrepresentation of severe psychopathology among the deceased subjects. However, we did not find relationship between paternal risk and death among the sons, indicating that genetic vulnerability did not contribute independently to premature death in this very small sample. It was striking that 66.7% of the deceased subjects vs. 12.0% of the survivors had been admitted to an psychiatric facility ($p < .001$). A logistic regression analysis showed that psychiatric hospitalization increased the risk of dying prematurely 5.3 times. These results illustrate that the most severe psychopathological cases in our sample had been eliminated at an early age, explaining the relatively small frequency of severe psychiatric diagnoses (i.e. schizophrenia, other psychoses and iv.drug abuse) found at age 30 and 40.

During the assessment at age 40, the interviewer (the author) was surprised by the high number of subjects, who reported that they had remitted from serious alcohol/drug addiction. The analyses confirmed this clinical impression: For alcohol *dependent* subjects, 56% HR and 55% LR subjects fulfilled DSM-III -R criteria for remission, while remission from alcohol *abuse* was reported by 91% HR and 80% LR subjects. The mean duration of remission from alcohol dependence was 11.1 years in the HR group vs. 11.3 years in the LR group, reflecting a stable remission without relapses and an increasing appreciation of a reasonable social and familial life style. Furthermore, 50-75% of the remitted alcoholics had recovered without any therapeutic intervention, suggesting that treatment is neither necessary or sufficient for resolution. In conclusion, paternal alcoholism is significantly associated with the development of alcoholism, but not its remission. These divergent results suggest several theoretical considerations: A family history of alcoholism may reflect a broad "proxy" for multiple diverse influences that, under certain circumstances, can result in alcoholism. In a health care context, the traditional view on alcoholism as an ongoing, continuous, progressive disease should be revised in direction of subtyping alcoholism in a "malignant" and "benign" form. For long time the distinction between benign and malignant manifestations in cancer disease has been recognized as a indispensable concept in a epidemiological, preventive, diagnostic, therapeutic and prognostic context. Based on the results from the 40 year follow-up about remission vs. current alcoholic drinking it is our suggestion to introduce a new method of subtyping of alcoholism into a "malignant" and "benign" form. It is obvious that such a distinction should be based on solid research results. At the present, we analyze which variables from the premorbidly collected data predict a malignant vs. benign outcome. The identification of such predictors (unique or in combination) will play an important role in the planning of preventive efforts and treatment programs.

A major result from the 40 year follow-up is the fact that the combination of premorbid ADHD and CD was an especially strong predictor of adult alcohol dependence among men, while paternal risk played a less substantial predictive role. We suggest that paternal risk probably serves as a broad proxy for multiple endophenotypes that are more directly associated with the development of alcoholism. Several studies have demonstrated a strong relationship between these two childhood disorders and later alcoholism [98, 105, 106].

A unique feature of our prospective study is its long duration, and the fact that the subjects were selected from a large birth cohort. Despite the strong correlation between childhood ADHD and CD, the multiple regression analysis showed that both independently predicted lifetime alcoholic severity. However, the two conditions in combination appeared to be even stronger premorbid markers of adult alcoholism than either condition alone. Like Flory and Lynam [98] we suggest that both childhood disorders reflect a central deficit responsible for impulse dyscontrol, beginning in early life, that is associated with alcoholic drinking. The results suggest that it may be useful to subtype young individuals with ADHD and CD for the purpose of applying specific, targeted intervention programs designed to minimize alcoholism later in life. In other words, such tailored interventions might be offered this young risk group to help them resist impulsive reactions and learn to use alcohol wisely. Also the mild cognitive impairment found in the 18-19 year assessment [74] had a considerable predictive role for alcoholism later in life [96]. Thus, impulse deregulation and disturbance in executive cognitive functioning may represent potential endophenotypes for alcoholism.

6. SUMMARY AND CONCLUSIONS

The present thesis is based on a selection of seven publications from The Danish Longitudinal Study of Alcoholism that cover all phases of the study from pregnancy to age 40. The long-term study was originally designed to identify premorbid predictors of alcoholic drinking in adulthood. The high-risk methodology was chosen to compare two groups of boys on many dimensions, before any of them had developed alcoholic problems. Sons of fathers treated for alcoholism represented the high risk (HR) group; sons of fathers never treated for alcoholism represented the low risk (LR) group.

The primary aim of the study were to identify premorbid measures that distinguished HR and LR sons, before alcoholic drinking had developed. Next step was to determine which of these premorbid risk markers also predicted alcohol dependence later in life, and to establish which risk markers in combination with alcohol dependence also predicted the course of alcoholism once it began (remission vs. non-remission). The main outcome measure was DSM-III-R alcohol abuse and dependence.

The subjects were selected from a Danish cohort of children born 1959-91, including 9,125 consecutive deliveries at the National University Hospital (Rigshospitalet) in Copenhagen. Earlier adoption studies on alcoholism have demonstrated a significantly increased risk among sons of alcoholic fathers for getting alcoholic themselves, independently if they were raised in the alcoholic biological family or in a non-alcoholic adoption family. Consequently, the approx. 18,000 parents were searched for serious alcoholic diagnoses in the Danish Psychiatric Register and the Copenhagen Alcohol Clinic. In this way, we identified 448 (5.3%) fathers who had been admitted and treated for serious alcoholic problems. Their 223 HR sons were available for the study. The HR boys were matched pairwise according to age, parity number, mothers age and fathers socio-economic status and matched with 106 boys (LR group) without parental registered alcoholism. No significant differences were found between the HR and LR group according to the five matching criteria, making them compatible. Daughters were not included in the study due to the relatively

low prevalence rate of female alcoholism. In a high-risk research connection it would have required an unrealistic huge sample to achieve a reasonable number of alcoholic women in adulthood.

Recognizing that alcoholism is a condition with a complex and partly unknown etiology, that spans across genetic, psychological and social elements, we selected fairly multidisciplinary and solid hypotheses, variables and instruments from the initiation of the study. During the years, several special scales were constructed to refine the analyses of the predictive power of the premorbid factors. The longitudinal study includes a premorbid assessment at age 18-19 and follow-up examinations at age 30 and 40. In addition, perinatal variables, data from the school period and archival data sources are included in the study.

The results from the *perinatal* period have shown that several measures are both distinguishing the two risk groups and possess predictive power according to alcohol dependence in adulthood. Birth weight, early weaning, postnatal non-supplement of vitamin K and cerebellar dysfunction in early childhood independently predict alcohol dependence at age 30 and 40.

In general, the schoolteachers reported that the HR boys had poorer achievement in *school* compared to the LR boys: more school changes, repeating a grade, lower number of grades completed, referrals from school psychologist to special classes and extra tutoring. Specifically, the HR boys had significantly more problems with impulsivity/restlessness and verbal proficiency when compared to the LR boys. Both the cognitive and behavioural problems in school point in the direction of ADHD and CD diagnoses as putative predictive factors for alcoholism in adulthood.

The premorbid assessment at *age 18-19* resulted in a series of significant HR-LR differences: The HR group had experienced more disrupted family conditions, stressful life events, parental crises and critical economic periods in the upbringing home compared to the LR group. In general, little psychopathology was found among the 204 participating young men in both risk groups.

The assessment was intended to be premorbid and even if the alcohol consumption the past week was relatively high (mean 17 drinks/week) the level was equal in both risk groups and also close to the mean consumption in the Danish general population of males at the same age. No subject met the DSM-III-R criteria for alcoholism in their late teens indicating that the assessment was truly premorbid.

The neuropsychological testing showed that the HR group had poorer scores than the LR group on tests on vocabulary skill, abstraction and planning abilities. These deficits may have rendered the HR group more vulnerable to psychosocial stress and subsequent alcoholic problems.

An alcohol challenge test during EEG and VEP recording showed that the HR groups self-rating of intoxication and physical symptoms were significantly lower than those of the LR group, even if there were no differences between the risk groups according to blood alcohol concentration.

A total of 68 variables distinguished the HR and LR groups at the $p < .05$ level of significance. In most of the comparisons, the HR group demonstrated the greatest degree of dysfunction, before alcohol drinking had become a problem.

The follow-up assessment at age 30 was organized as clinical interviews in the subjects home or at IPM. The interviewer was blind with respect to the subjects' assignment to the HR or LR group. We intended to use measures covering the same domains as we used in the premorbid assessment 10 years earlier. The Psychiatric Diagnostic Interview (PDI -IV) was used as a fully operationalized and DSM-III -R criterion-referenced instrument covering 20 basic psychiatric syndromes. The primary purpose was to examine which of the variables that distinguished the two risk groups at age 18-19, also predicted DSM-III -R diagnoses of alcohol abuse/dependence at age 30. As described in section 3.4.6, data reduction and a multivariate analysis was used to identify those putative markers that maximized the predictive power of alcohol abuse/dependence at age 30. This "winnowing" process resulted in 394 variables, that were tested for premorbid HR vs. LR differences and +/- alcohol abuse/dependence at age 30. The final list of putative markers resulted in 12, most strongly associated with number of lifetime drinking problems (see section 4.4).

At age 30, 41% HR vs. 28% LR subjects were assigned a DSM-III-R diagnosis of alcohol abuse/dependence. However, it was only alcohol *dependence* (29% HR vs. 15% LR, $p = .02$) that significantly distinguished the two risk groups. As it appears from table 7, alcohol *abuse* was almost equally distributed in the two groups (19% HR vs. 16% LR). The elevated levels of alcoholism in this sample is largely due to the initial matching strategy, resulting in a slightly skewed predominance to the lower end of the Danish socioeconomic spectrum.

The two risk groups did not differ significantly concerning other psychopathology than alcohol-related diagnoses. However, when the sample was grouped according to alcohol use disorders, the majority of psychopathology was found in the dependence group. Most striking is the co-morbid correlation between dependence and antisocial personality disorder (ASPD), ($p = .001$).

The identification and validation of putative markers was based on 68 variables from the 18-19 year assessment that distinguished the HR and LR group. Of these 68 variables, 27 of them also distinguished subjects with and without a DSM-III-R diagnosis of alcohol abuse/dependence at age 30 (see Table 9). Next step was to identify final predictors that were most strongly associated with number of lifetime drinking problems at age 30. This resulted in elimination of 16 variables, leaving 12 final predictors, shown in Table 10. A standard multiple regression analysis showed that only four variables contributed significantly to the outcome prediction of alcoholic drinking: ASPD uniquely accounted for 7% of the variance, number of life crises accounted for 6%, low birth weight for 4% and rating of childhood unhappiness for 3% of the drinking outcome measure. Altogether, 46% of the variance in the lifetime drinking severity measure was "explained" by the model. Only a few other premorbid HR-LR differences were associated with alcohol dependence at age 30: Word Fluency and no.of errors in the Porteus Maze Test from the initial neuropsychological test battery.

In conclusion, the results from the 30 year follow-up examination provide broad support for models emphasizing the cumulative effect over time of internal and external variables in biologically vulnerable individuals. In particular, emotional and behavioural deregulation (CD and ASPD) in childhood seem to be potent predictors of male alcoholism, even more potent than genetic influence.

The follow-up assessment at age 40 includes analyses of prediction of mortality, clinical course and remission rates and childhood ADHD and CD as predictors of alcoholic drinking.

Concerning *mortality,* we identified 21 deceased subjects at an average age of 31. The standardized mortality rate in the sample was significantly increased (6.38%, $p < .003$) when compared to Danish age- and gender corrected mortality rate (2.17%). The causes of death among the 21 subjects were similar to those in

the Danish male population at age 40. Data from the Danish Psychiatric Register and the Danish Causes of Death Register revealed severe psychiatric morbidity at a relatively young age for those who later died.

We did not find significant differences between HR and LR subjects, indicating that genetic vulnerability did not contribute independently to premature death. Analyses comparing death (n = 21) and survival subjects (n = 308) showed that 66.7% of the deceased subjects vs. 21% of the survivors had been hospitalized in a psychiatric facility ($p < .001$), indicating that severe psychiatric morbidity at an young age predicted premature death.

Clinical course and remission of alcoholic drinking: The HR group was significantly more likely to develop alcohol dependence (29%) than the LR group (15%), ($p = .02$), while there were no group differences regarding alcohol abuse. Measures of lifetime MAST scores and search in the Danish Psychiatric Register confirmed this finding of overrepresentation of alcoholism among the HR subjects.

As it appears in Table 14, we found a relatively high remission rate both in the HR and LR group, now 40 years of age. The mean duration of remission from alcohol dependence was 11.1 year in the remitted HR group and 11.3 year in the remitted LR group. Of the 52 remitted alcohol-dependent subjects only 62% reported that they had received treatment opposed to 18 of the 22 (82%) non-remitted dependent, suggesting that treatment is not associated with remission. These results suggest several theoretical considerations: A family history of alcoholism may reflect a broad "proxy" for multiple diverse influences that under certain circumstances, can result in alcoholism. The traditional view on alcoholism as a chronic, invalidating disease should be revised in direction of subtyping alcoholism in a "malignant" and "benign" form with different consequences for course, choice of treatment modality and prognosis.

Childhood ADHD and CD as predictors for alcoholism at age 40: Several studies have demonstrated that alcoholic drinking in adulthood is often preceded by CD and ADHD in childhood. In our long-term study three premorbid predictors have been used: Risk status, childhood ADHD and CD. They have been correlated to the outcome measures of DSM-II-R alcohol dependence/abuse and life time alcoholism severity at age 30 and 40.

The ADHD scale was based on the school teacher questionnaire (see paper I), selected and validated resulting in a 12-item scale (Cronbach's alpha coefficient = .092). The CD scale was based on relevant questions from the social worker interview from the assessment at age 18-19. We found a highly significant correlation between the constructed CD-scale, ASPD derived from the PDI-R interview and the ADHD-scale mentioned above. Of the original subjects, a subsample of 110 had complete data from the two childhood scales and the alcoholism outcome measures from the follow-up examinations at age 30 and 40. In this subsample, paternal risk did not predict adult alcoholism outcome. Subjects who were above a median split on both the ADHD and CD scales, were more than six times more likely to develop alcohol dependence than those who scored below the median in both scales. Although the two childhood measures were closely correlated, a multiple regression analysis showed that each of them predicted measure of lifetime severity independently. It is concluded that ADHD combined with CD was the strongest predictor of alcohol dependence later in life.

In conclusion, the 40 year follow-up examination revealed several significant results: 1) An increased standardized mortality rate characterized by severe psychopathology among the deceased subjects, 2) a relative high remission rate in both risk groups and 3) a high predictability of adult alcohol dependence among subjects with CD and/or ADHD in childhood. While the development/occurrence of alcoholism seems to have a considerable genetic component, remission is correlated with environmental/social/cognitive influences.

7. FUTURE PERSPECTIVES

The Danish Longitudinal Study of Alcoholism has demonstrated the strength of applying the high-risk design into the field of alcoholism. Several premorbid measures from the perinatal period, school time and the 18-19 year assessment have shown their impact as powerful predictors of alcoholism later in life. In particular, the fact that *ADHD and CD* in childhood and adolescence belong to the strongest predictors point in the direction of implementation of educational, psychological and medical preventive intervention at an early stage of the boys life. However, such an initiative, even based on rational scientific evidence, is ethically controversial, because preventive efforts at the individual level is not fully accepted among parents, school teachers and public health professionals. It requires a more tolerant and understanding attitude in the general population to introduce preventive efforts for the parents to their son at high risk.

The results from the 40 year follow up assessment of a high proportion of *remission* from alcohol/cannabis dependence (with or without treatment intervention) is in accordance with Vaillants findings in his long term study [56, 57]. Our analyses have demonstrated that paternal risk concerning alcoholism has no significant influence on remission, while it indeed originally predicted the onset of alcoholic drinking in the son, a result similar to Vaillants findings. He has put this phenomenon like this: "The skill it takes to fall into a hole is not the same as the skill it takes to climb out" (GE Vaillant, personal communication 2004). The study group has recently initiated analyses on putative premorbid factors for remission vs. non-remission of alcoholic drinking in adulthood [96].

Our study is a "masculine" study having followed up only *sons* of alcoholic *fathers,* primary because the original adoption studies - pointed in the direction of a considerable genetic transmission from father to son, opposed to adopted-away daughters. The high prevalence of male alcoholism was another argument for focusing on the sons and not the daughters. Unfortunately, we did not have information on the pregnant mothers alcohol consumption. During the past decades an increasing alcohol consumption among Danish females has been reported, and the prevalence of female alcoholism is increasing. Consequently, future clinical/epidemiological alcohol research studies should include females, especially in a longitudinal connection. The only "mother-daughter" research project we are aware of is an Australian cohort study focusing on the predictive impact of in utero alcohol exposure on the offspring in early adulthood [64].

Our results indicate that alcoholism may come in two forms or subtypes: a "benign" subtype characterized by a stable remission from dependence at age 30-40, and a "malignant" subtype with a continued pattern of alcoholic drinking in spite of treatment/intervention efforts. Such a subtyping of disease is essential in the cancer field, both in diagnostic, therapeutic and prognostic connection. In the case of alcoholism, future research should focus on this important aspect, especially identification of early predictive factors for a "benign" vs. "malignant" outcome. Such a distinction will have obvious implications in the planning phase of

a treatment course. It is our suggestion that the described subtyping of alcoholism could be implemented in future editions of the DSM- and ICD classifications.

In this connection it should be mentioned that the study group plan *another follow-up* assessment when the subjects have reached the age of 50. We will examine if the described remission rate still is stable, how the pattern of co-morbidity has developed and also collect data on causes of death in the sample. We also discuss the possibility of extending the sample by including the subjects' offspring in the study. In case, we intend to include advanced molecular genetic techniques in both generations of subjects. But still it is important to include both biological, psychopathological and social factors due to the multifactorial and complex background of alcoholism.

Another advantage in the long-term prospective study is to examine putative *protective factors*, in particular among the non-alcoholic HR subjects who are characterized by an increased genetic vulnerability for future development of alcoholism. It would be important to examine the significance of the non-alcoholic HR group's resilience, i.e. to identify protective factors overcoming high genetic risk.

We have utilized the access to the Danish nationwide registries, primary to examine psychopathology (in particular alcoholism) among the non-participant subjects. In this connection, it is important to emphasize the validity of the *clinical diagnostic interview* as a precondition for correct evaluation of the subjects' psychopathology. It is tempting only to rely on archival data in cohort studies, but in the case of alcoholism only approx. 10-20% of the affected individuals will ever be registered as patients admitted to a psychiatric facility.

It is my hope that the results from our long-term study will inspire other research groups to take up the high risk concept, and that public health professionals will initiate the necessary discussion of the implementation of preventive efforts at the individual level in the case of subsequent alcoholism.

Ialt 241 (162 HR og 79 LR) forsøgspersoner deltog i denne efterundersøgelse, der omfattede sociale og kliniske interviews. Psychiatric Diagnostic Interview (PDI-IV) blev anvendt som diagnostisk instrument omfattende 20 DSM-III-R kategorier. Hovedformålet var at undersøge, hvilke HR-LR forskelle fra den præmorbide undersøgelse i 18-19 års alderen, der også havde størst prædiktiv betydning for alkoholafhængighed i 30-års alderen. Som forventet fandtes signifikant flere HR-personer med alkohol misbrug/afhængighed (41%) end blandt LR-personer (28%). Overordnet blev der fundet en høj frekvens af alkoholafhængighed i materialet (16.2%). Datareduktion og multivariate analyser blev anvendt for at maksimere prædiktiviteten af tidligere indsamlede præmorbide variable. Fire variable var uafhængigt af hinanden tæt korreleret med alkoholisk drikkemønster i 30 års alderen: Lav fødselsvægt, antal livskriser i barndommen, ulykkelig

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