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Cohort Profile: The DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980

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ABSTRACT

Purpose:

The DANLIFE cohort is a prospective register-based study set up to investigate the complex life course mechanisms linking childhood adversities to health and well-being in childhood, adolescence and young adulthood including cumulative and synergistic actions and potentially sensitive periods in relation to health outcomes.

Participants:

All children born in Denmark in 1980 onwards have successively been included in the cohort until the end of 2015 totalling more than 2.2 million children. The study population has continuously been followed in the nationwide Danish registers for an average of 16.8 years with full data coverage in the entire follow-up period.

Findings to date:

DANLIFE provides information on a wide range of family-related childhood adversities with important psychosocial implications for health and well-being in childhood, adolescence and young adulthood. Measurement of covariates indicating demographic, social and health-related factors have also been included from the nationwide registers. In this cohort profile we provide an overview of the childhood adversities and covariates included in DANLIFE. We also demonstrate that there is a clear social gradient in the exposure to childhood adversities confirming clustering of adverse experiences within individuals.

Future plans:

The DANLIFE cohort provides a valuable platform for research into early life adversity and opens unique possibilities for testing new research ideas on how childhood adversities affect health across the life course.

Strengths and limitations of this study

- DANLIFE provides an unselected data source for investigation of the effects of a wide range of objectively measured childhood adversities on health outcomes in childhood, adolescence and young adulthood.
- The large sample size including all children born in Denmark between 1980 and 2015, totalling more than 2.2 million children, allows for the assessment of new research ideas addressing rare outcomes and complex mechanisms such as cumulative and synergistic actions and potential sensitive periods.
- The unique identification number given to all Danish residents enables linkage of information from any Danish register or existing cohort to DANLIFE, providing opportunities to answer a wide range specific research questions.
- The measures of childhood adversities and health-related outcomes in DANLIFE are objective but crude and may be vulnerable to misclassification.

INTRODUCTION

The fact that many adulthood diseases have roots in earlier life is by now quite well documented and hardly debatable. The life course approach to studying health, which has increasingly been gaining attention in the past two decades, acknowledges the long-term biological, psychosocial and behavioural processes that operate across the life span, linking earlier life exposures to health in later life.[1] These processes are extremely complex and far from being fully elucidated, but a growing amount of evidence suggests that childhood may constitute a period when the exposure to psychosocial adversities is particularly detrimental for future health and developmental trajectories. Advances in neuroscience, molecular biology, and epigenetics have put forward an intriguing hypothesis that adverse events experienced early in life, when the human stress response system is still under development, may produce long-lasting alterations in the way the brain and the body respond to stress.[2,3] These alterations, which can be traced not only on the behavioural, but also on

the epigenetic level,[4] are, on one hand, an adaptation to a stressful environment; on the other hand, they may have long-lasting costs to future mental health and the normal regulation of the metabolic and cardiovascular systems, leading to physical health consequences.[5]

Given that childhood may constitute a sensitive period for a whole range of exposures, including the exposure to stress, the timing of these exposures is central to life course epidemiology. The vast majority of the previous studies on childhood stress and health outcomes are, however, limited by the retrospective design, where middle-aged men and women are asked to retrospectively recall childhood events. Such a design suffers from a recall bias, since the recollection of the events, and especially of when they happened, will often be inaccurate. Furthermore, such a study design will typically ignore any effects of childhood adversities on health outcomes in early adult life and may severely underestimate the health effects associated with such events. Finally, most of the previous studies only include one or two childhood adversities, but it is well known that social disadvantages such as parental unemployment, economic hardship, bereavement, and parental drug- or alcohol abuse tend to cluster.[6] Researchers in child development have long argued that while exposure to a single risk factor hardly ever causes enduring harm, experience of multiple risk factors often has consequences for health.[7,8] Thus, studies of single risk factors in isolation will underestimate their effects. Research on adversity needs to account for the accumulation of stressors from different domains as well and across the life span.[9,10] More comprehensive measures of timing and accumulation of stress focusing specifically on childhood are therefore needed to bring this area of research forward.

The empirical testing of the hypotheses regarding the exact timing of exposures as well as the cumulative and interactive effects of stressors requires large data materials with frequent repeated measures over time. There is a growing number of birth cohorts and other longitudinal studies with rich repeated information designed particularly for such research, e.g. the British birth cohorts.[11–14]

While these cohorts provide a key platform for life-course research, they often encounter several important methodological problems. First, the measurements are not always repeated frequently enough to test elaborate hypothesis regarding the timing of exposures. Second, exposures are likely to interact with one another[9] and the existing cohorts often do not have enough statistical power to test complex interactions. Finally, the existing cohort studies encounter massive problems related to selection bias into and out of the cohorts[15], which may severely bias the estimates. Retrospective self-reports of adverse childhood experiences have recently been shown to be strongly associated with non-response and loss to follow-up, and the missing data are unlikely to be missing at random.[16]

The DANLIFE cohort was established to provide a unique source of information on how childhood adversities affect health across the life course. The DANLIFE cohort addresses the abovementioned methodological problems by utilizing unique unselected data from nationwide registers covering all children born in Denmark since 1980, totalling more than 2.2 million children. All data on major life events, social adversity and health outcomes are routinely collected and continuously updated for all children included in the cohort. The precise recording of timing of the information in DANLIFE enables the assessment of temporality between exposures, outcomes and covariates as well as identification of potential critical and sensitive periods of exposure to childhood adversities. The cohort was specifically set up to test hypotheses on complex life course mechanisms including:

a) Investigating whether specific childhood adversities act independently, cumulatively or synergistically on clinical health outcomes across life stages
b) Identifying potentially sensitive periods (e.g. infancy, childhood, adolescence, early adulthood) for childhood adversities in relation to health outcomes

The DANLIFE cohort is placed at a secure server at *Statistics Denmark*. Access to Danish administrative and health registers is granted by *Statistics Denmark* and *The Danish Health Data Authorities*. Data is provided for research purposes in an anonymous and secure form.

COHORT DESCRIPTION

Study population

All Danish residents are given a unique 10-digit civil personal registration (CPR) number upon immigration or at birth, as do non-resident persons who become members of the Danish Labour Market Supplementary Pension Fund or pay taxes in Denmark.[17] The CPR-number permits exact linkage on individual level between national administrative, clinical, and health research registries in Denmark.[17] Valid and continuously updated information on many socioeconomic, demographic, and health-related factors from the Danish nationwide registers were provided by Statistics Denmark and the Danish Health Data Authorities to DANLIFE. All children born in Denmark in 1980 or thereafter to mothers who had a CPR-number at the time of birth have been identified in the Danish Civil Registration System (CRS)[17] and have successively been included in DANLIFE. Since the data from CRS provided to DANLIFE is updated annually and includes the population on the 1st of January each year, children who are live-born but die or emigrate within the same calendar year are not included in the data from CRS. Children who died or emigrated in their first year of life were instead identified in the Medical Birth Registry (MBR)[18] (n=13,756). In the period 1980-1996, MBR included all children born in Denmark to mothers with residency in Denmark at the time of birth. Since 1997, MBR includes all births taking place in Denmark by mothers who already have a CPR-number.[17,18] Immigrants not born in Denmark are not included in the DANLIFE cohort because no information on childhood adversities is available for immigrants prior to immigration.

The study participants have been followed until emigration, death or the end of follow-up on the 31st of December 2015. The DANLIFE cohort includes 2,223,927 persons followed for an average of 16.8 years corresponding to more than 37 million person-years (Figure 1). Persons emigrating during follow-up (n=164,348; 7.4%) are censored at the date of emigration and are not re-entered into the cohort if ever returning to Denmark, since there would be an information gap in the period the

person spent outside of Denmark. Censoring on date of death was possible using information from CRS (n=20,514; 0.9%).

Family linkage

The CPR-numbers of the parents in DANLIFE have been retrieved from the child's first year of life from CRS supplemented by information from MBR. The parents registered in CRS are the legal parents and biological parents can therefore not be distinguished from adoptive parents.[17] However, the number children who are born in Denmark and adopted during their first year of life is less than 0.1% according to official statistics. The parents registered in MBR are assumed to be the biological parents.[18] The CPR-numbers of the parents were used to identify siblings as persons linked to the same mother and father and to identify twins as persons born to the same mother on the same day (+/- 1 day). The CPR-number of the parents can also be used to identify siblings who only share one parent. The linkage to parents and siblings in DANLIFE enable identification of exposure to a range of family-related childhood adversities, such as severe illness in the family. The family linkage also enables identification of family history of specific diseases through linkage to the Danish National Patient Registry.[19] Children with missing information on both parents in both CRS and MBR were not included in the DANLIFE cohort (n=3103), since it would be impossible to identify the siblings of these children as well as the exposure to most of the family-related childhood adversities.

Follow-up

The registers combined in DANLIFE are updated for research purposes once a year. To date, the DANLIFE cohort includes information from the 1st of January 1980 until the 31st of December 2015, and will continue to be updated as children are born and registered. The continuity of the Danish registries provides full data coverage in the entire follow-up period, except for information on family poverty which is based on the household equivalised disposable income, which was only available from 1987 onwards. Most factors have been specified with an exact date such as date of birth, emigration, death, highest attained education and all somatic and psychiatric diagnoses registered in

the National Patient Registry.[19] Information on personal income and transfer payments[20], labour market affiliation[21] and parental separation[17] are registered across a given calendar year and the timing of these adversities is therefore set to the year of occurrence (Table 1). Since the objective of the DANLIFE cohort is to enable assessment of the effects of adversities experienced in childhood on health and well-being, we restricted the exposure period to 0-18 years of age. The exposure period can easily be altered to accommodate research projects with alternative objectives.

Childhood adversities and covariates

The uniqueness of DANLIFE lies within the definition and construction of measures of selected childhood adversities with important psychosocial implications for health and well-being in childhood, adolescence and young adulthood. In childhood, the family environment plays a crucial role for development and well-being. At the same time, a straining family environment, and the social circumstances in which it takes place, may be major sources of stress in children.[9,22–25] Two aspects of family environment that have been shown to be important sources of stress in children are lack of responsive caregiving[2,26,27] and loss, or the threat of loss, within the family.[25,27–29] Social disadvantage in the family is also a source of stress in children as it may affect parenting skills and family climate, as well as the availability of social and material resources, such as high quality housing, proximity of good schools and recreation areas, etc.[30–32] The linkage between child, parents and siblings in DANLIFE enables measurement of a range of childhood adversities that are likely to affect the quality of caregiving (i.e. being placed in foster care, parental psychiatric illness, sibling psychiatric illness, and parental alcohol or drug abuse); indicate loss, or the threat of loss, within the family (i.e. parental somatic illness, sibling somatic illness, parental separation, and death of a parent or a sibling) and social disadvantage (i.e. family poverty and parental long-term unemployment). Table 1 provides an overview of the adversities included DANLIFE.

Table 1 Definition and timing of the childhood adversities included in the DANLIFE cohort

Adversity	Definition	Date
Foster care	Being placed in out-of-home care	Date of placement
Parental psychiatric illness	A parent's admission for at least one day with an ICD-8 or ICD-10 code related to psychiatric illness. ICD-8 codes: Psychoses (290-299 except 291); Neuroses, personality disorders and other nonpsychotic mental disorders (300-309 except 303-304); and Mental retardation (310-315); ICD-10 codes: Mental, behavioural and neurodevelopmental disorders (F00-F99 except F10-F19)	Date of diagnosis
Sibling psychiatric illness	A sibling's admission for at least one day with an ICD-8 or ICD-10 code related to psychiatric illness. ICD8 codes: Psychoses (290-299); Neuroses, personality disorders and other nonpsychotic mental disorders (300-309); and Mental retardation (310-315); ICD10 codes: Mental, behavioural and neurodevelopmental disorders (F00-F99)	Date of diagnosis
Parental alcohol abuse	A parent diagnosed with an illness related to alcohol abuse or receiving a prescription of a drug used in treatment of alcohol addiction. ICD-8 codes: Alcoholic psychosis (291); Alcoholism (303); Alcoholic cirrhosis of the liver (571.09); Alcoholic steatosis of the liver (571.10); ICD-10 codes: Alcohol psychosis and abuse syndrome (F10); Alcoholic polyneuropathy (G62.1); Alcoholic cardiomyopathy (I42.6); Alcoholic-induced acute (K85.2) and chronic (K86.0) pancreatitis; Alcoholic liver disease (K70); Alcoholic gastritis (K29.2); ATC codes: Drugs used in alcohol dependence (N07BB)	Date of diagnosis/ prescription
Parental drug abuse	A parent diagnosed with an illness related to drug abuse or receiving a prescription of a drug used in treatment of drug addiction. ICD-8 codes: Drug dependence (304); ICD-10 codes: Opioids (F11); Cannabinoids (F12); Sedatives/hypnotics (F13); Cocaine (F14); Other stimulants (F15); Hallucinogens (F16); Other and multiple drugs (F18-F19); ATC codes: Drugs used in opioid dependence (N07BC)	Date of diagnosis/ prescription
Parental separation	Separation of the parents	Year of separation
Parental death	Death of a parent	Date of death
Sibling death	Death of a sibling	Date of death
Parental somatic illness	A parent diagnosed with one of the ICD-8 codes included in the Charlson comorbidity index[33] in the period 1980-1993 or the ICD-10 codes included in the updated version of the Charlson comorbidity index[34] in the period 1994-2015	Date of diagnosis
Sibling somatic illness	A sibling diagnosed with one of the following somatic illnesses related to mortality in children aged 0-18 years (ICD-8/ICD-10 codes): Malignant neoplasm (140-199/C00-C96); Congenital anomalies of the heart and circulatory system (746-747/Q20-Q28); Congenital anomalies of the nervous system (743/Q00-Q07); Cerebral palsy (343-344/G80-G83); Epilepsy (345/G40-G41); Cardiomyopathy (425/I42-I43); Congenital disorders of lipid metabolism (272/E75)	Date of diagnosis
Parental long-term unemployment	A parent being unemployed for at least 12 months within two consecutive years	First year of unemployment
Poverty	Family income below 50% of the median national family income in a given year, in three consecutive years	Third consecutive year of poverty

An important and growing field within the life course framework is the assessment of mediation and interaction.[1] The following covariates for confounding, mediation and interaction assessment have been incorporated in DANLIFE so far: sex (*male*, *female*), age at any given time (based on date of birth), parental highest attained education at the time of birth (*low* ≤ 9 years i.e. mandatory

education in Denmark; *middle* 10-12 years i.e. youth education and vocational education; and *high* >12 years), birth order, birth weight (in grams), parental age at any given time (based on date of birth) and ethnicity (*Danish, non-Danish* if at least one parent has a nationality other than Danish). The definitions of the covariates can be altered to accommodate specific research objectives. In principle, the CPR-number enables the inclusion of information on exposures, outcomes and covariates from any Danish register or selected study population into the DANLIFE cohort given granted permission from the authorities responsible for data security. An overview of the nationwide registers that have been linked in the DANLIFE cohort and which specific adversities and covariates each register has provided information on is shown in Figure 2. Information from several registers has been combined to define the adversities representing parental alcohol and drug abuse (Table 1 and Figure 2).

FINDINGS TO DATE

DANLIFE is a newly established cohort and no results based on its data have therefore been published to date but several studies investigating the effect of childhood adversities on health outcomes such as cardiovascular disease, type 1 diabetes and all-cause mortality are ongoing. Table 2 gives an overview of the exposure to the specific childhood adversities in the total study population of more than 2.2 million children. Parental separation was the most frequently experienced adversity during follow-up (29%) followed by parental long-term unemployment (25%). In this large study population, several thousand had experienced even the rarest adversities (i.e. sibling death and sibling psychiatric illness). Table 2 further shows a clear social gradient in the exposure to childhood adversities in the DANLIFE cohort. The proportions of children exposed to the specific childhood adversities are consistently increasing with decreasing levels of maternal education measured at the time of birth. The gradient is strong for the adversities reflecting family poverty, parental unemployment, and parental alcohol and drug abuse. The social gradient is also pronounced for parental separation where as many as 40% of the children born to mothers with a low level of education have experienced separation compared with only 19% of the children born to mothers

with a high level of education. The social gradient is evident for all childhood adversities included in the cohort.

Table 2 Exposure to specific childhood adversities according to maternal educational level

			Maternal education[a],[b]					
	Total		High		Middle		Low	
Adversity	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**2,223,927**	**100.0%**	**714,718**	**32.1%**	**869,775**	**39.1%**	**571,161**	**25.7%**
Foster care	66,069	3.0%	4,120	0.6%	13,087	1.5%	45,936	8.0%
Parental psychiatric illness	89,014	4.0%	15,501	2.2%	30,072	3.5%	40,953	7.2%
Sibling psychiatric illness	18,213	0.8%	4,133	0.6%	6,287	0.7%	7,294	1.3%
Parental alcohol abuse	146,186	6.6%	22,798	3.2%	49,422	5.7%	70,640	12.4%
Parental drug abuse	40,248	1.8%	4,707	0.7%	11,622	1.3%	22,694	4.0%
Parental separation	638,879	28.7%	136,615	19.1%	259,465	29.8%	230,359	40.3%
Parental death	55,759	2.5%	11,605	1.6%	19,083	2.2%	23,453	4.1%
Sibling death	10,543	0.5%	2,516	0.4%	4,001	0.5%	3,679	0.6%
Parental somatic illness	270,529	12.2%	71,529	10.0%	103,317	11.9%	89,314	15.6%
Sibling somatic illness	56,911	2.6%	15,793	2.2%	22,170	2.5%	17,694	3.1%
Parental long-term unemployment	558,534	25.1%	80,636	11.3%	201,602	23.2%	259,686	45.5%
Family poverty[c]	99,457	5.4%	13,655	1.9%	34,421	4.0%	46,338	8.1%

[a]Missing information on maternal education, n=68,273 (3.1%)
[b]High: >12 years; Middle: 10-12 years; Low: ≤9 years
[c]From 1987 onwards, total n=1,846,564

The accumulation of childhood adversities in the DANLIFE cohort is presented in Table 3. Almost half of the study population did not experience any childhood adversities during follow-up and almost 10% had experienced three or more adversities. The previously mentioned well-known clustering of social disadvantage can also be seen in Table 3. More than 60% of the children born to mothers with a high level of education at the time of birth have not experienced any adversities during follow-up compared with only 25% of the children born to mothers with a low level of education. Accordingly, only 3.5% of the children born to highly educated mothers have experienced three or more adversities compared with 20% of the children born to mothers with a low educational level. This is also reflected in the average numbers of adversities experienced during follow-up among children born to mothers with a high (0.5), middle (0.9) and low (1.5) level of education.

Table 3 Accumulation of childhood adversities according to maternal educational level

			Maternal education[a,b]					
	Total		High		Middle		Low	
Adversities	N	%	N	%	N	%	N	%
0	1,035,594	46.6%	449,025	62.8%	400,264	46.0%	147,138	25.8%
1	651,608	29.3%	181,006	25.3%	276,572	31.8%	179,500	31.4%
2	324,057	14.6%	59,621	8.3%	127,221	14.6%	129,297	22.6%
3+	212,668	9.6%	25,066	3.5%	65,718	7.6%	115,266	20.2%
Total	**2,223,927**	**100.0%**	**714,718**	**32.1%**	**869,755**	**39.1%**	**571,161**	**25.7%**
Mean no. adversities			0.5		0.9		1.5	

[a]Missing information on maternal education, n=68,273 (3.1%)
[b]High: >12 years; Middle: 10-12 years; Low: ≤9 years

STRENGTHS AND LIMITATIONS

The main strengths of DANLIFE include the unselected sample and the large sample size. The unselected sample ensures unbiased estimates of the effects of adversity on clinical outcomes, and the large sample size and linkage to medical registers give the possibility to study very rare health outcomes, including possibilities for interaction analyses, which tend to require a lot of statistical power. Yearly updated information provides higher time resolution than most available birth cohorts and allows for estimation of exposure trajectories (i.e. moving in and out of poverty) and rather precise timing of exposures, which is crucial for investigation of critical and sensitive periods. Finally, information about exposures and outcomes that comes from registers is more objective than questionnaire-based data, as they are not subject to recall bias and other type of biases that are associated with self-reporting (e.g. participants' personality affecting their over-reporting of symptoms).

The DANLIFE sample is still very young, with a maximum age of 36 years, and therefore quite healthy. Even though many diseases will not be manifested until a later age, we still observe more than 20,000 deaths and a considerable number of clinical outcomes such as cardiovascular disease, type 1 diabetes and sub-types of cancer in the DANLIFE sample. Thus, the large sample size provides a

unique opportunity to evaluate effects of childhood adversities on clinical health outcomes in early adult life, which is a severely understudied area due to lack of statistical power and few cases in previous life course studies.

On the other hand, defining exposures and outcomes based on registers has important trade-offs. With respect to outcomes, only clinical diagnoses are available for investigation. This for example means that only severe mental health problems resulting in hospital admission will be captured in the data. Similarly, many relevant exposures related to family dynamics and sensitive care cannot be measured using registers. Furthermore, those measures that can be defined via registers are crude and may be vulnerable to misclassification. To illustrate, the effects of parental separation on children's well-being may be modified by a large number of circumstances, such as the extent to which parents are able to collaborate post-divorce and the shared custody arrangement. It may also be important whether parents enter new relationships once their marriage is dissolved. This information can only to a very limited degree be obtained via registers. As an example of possible misclassification, parental psychiatric illness, which may be severe enough to affect the family functioning, but not severe enough to result in hospitalization, will not be captured in registers.

However, the limitations concerning crude or incomplete measures can be overcome if DANLIFE data are combined with more precise questionnaire based measures: because the CPR-number is available for all participants, it is possible to link DANLIFE to other existing cohorts or to invite a sub-sample of those who are in the DANLIFE cohort for a more detailed assessment. Thus, the DANLIFE cohort provides a valuable platform for research into early life adversity and opens a lot of unique possibilities for testing new research ideas.

COLLABORATION

Access to the Danish register data must be granted by Statistics Denmark and The Danish Health Data Authorities and is therefore not open access. Access to the established DANLIFE cohort is available to other investigators through collaborative agreements and a secured access. Please contact Professor Naja Hulvej Rod [nahuro@sund.ku.dk] for further information.

FURTHER DETAILS

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Author statement

All authors were involved in the conception and design of the study. JB were responsible for data management and analyses. All authors contributed to the writing of the manuscript and have critically revised and approved the final version.

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Competing Interest

None declared.

Data sharing statement

Access to DANLIFE is available through collaborative agreements and granted access to the Danish registers by Statistics Denmark and The Danish Health Data Authorities. Please contact Professor Naja Hulvej Rod [nahuro@sund.ku.dk] for further information.

Figure 1 Characteristics of the DANLIFE study population and follow-up period

Figure 2 Nationwide Danish registers linked on individual level in the DANLIFE cohort using the Civil Personal Registration (CPR) number and the information they provided to the cohort

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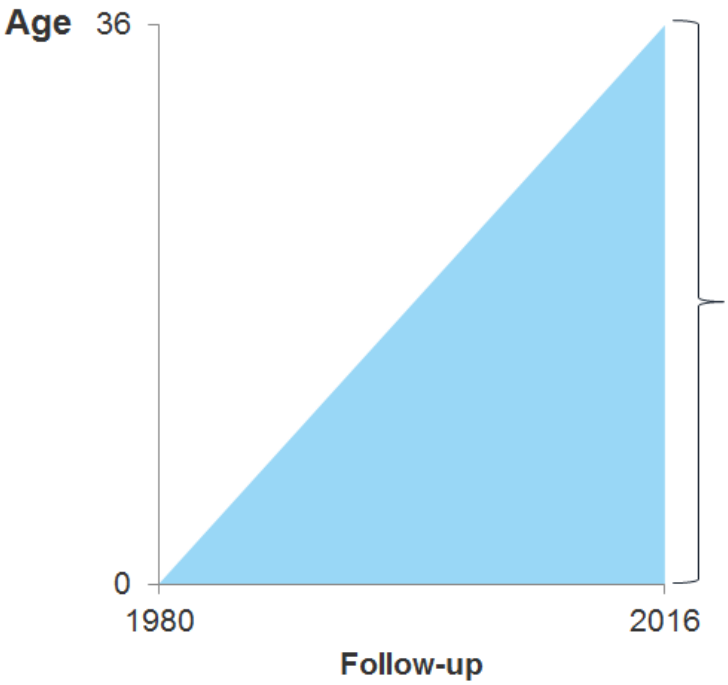
Study population: DANLIFE



Total N: 2,223,927

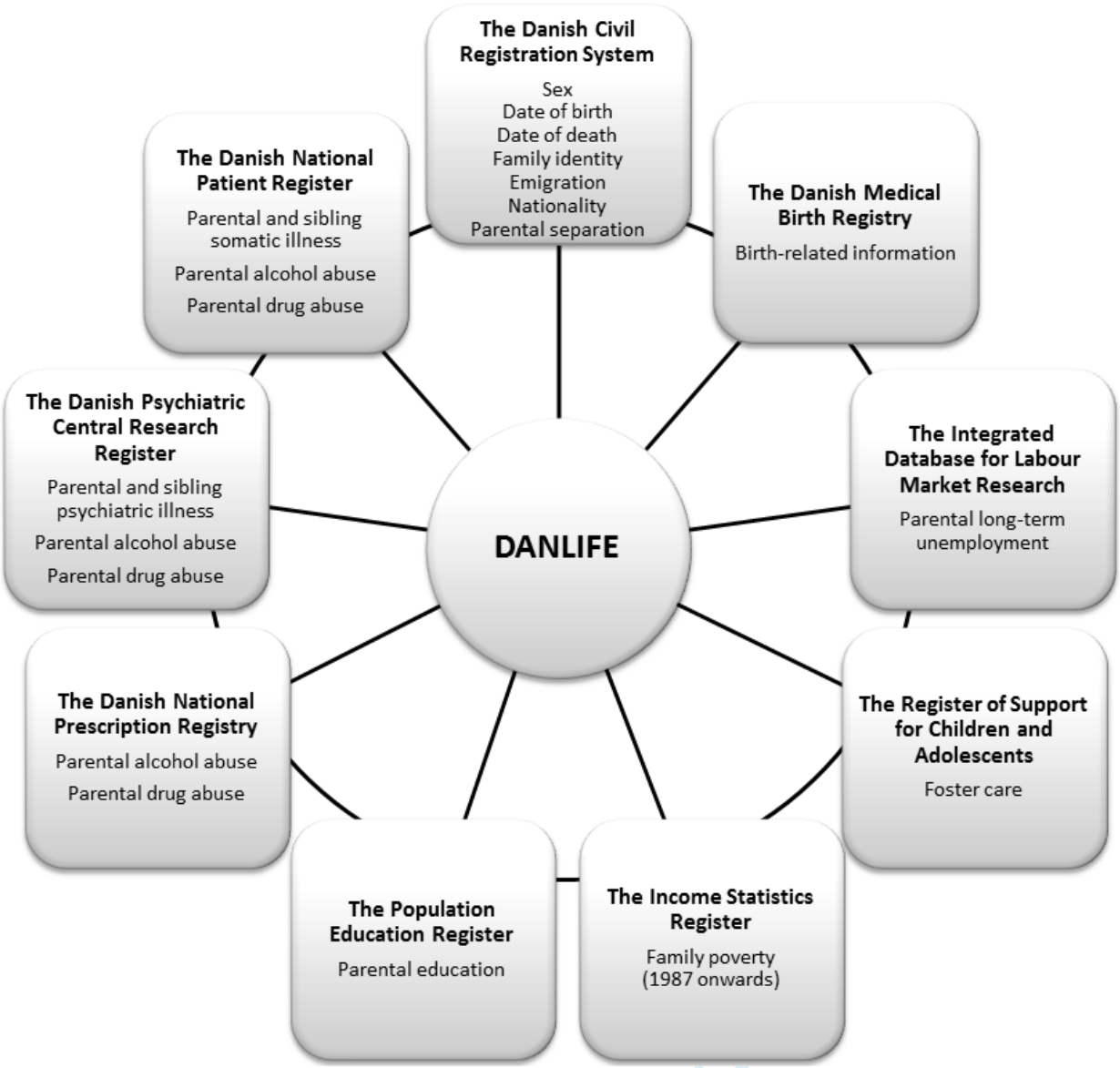
Deaths: 20,514 (0.9%)

Emigrations: 164,348 (7.4%)

Person years: 37.3 million

Mean follow-up: 16.8 years

Males: 51.3%


The Danish Civil Registration System
Sex
Date of birth
Date of death
Family identity
Emigration
Nationality
Parental separation
The Danish National Patient Register
Parental and sibling somatic illness
Parental alcohol abuse
Parental drug abuse
The Danish Medical Birth Registry
Birth-related information
The Danish Psychiatric Central Research Register
Parental and sibling psychiatric illness
Parental alcohol abuse
Parental drug abuse
DANLIFE
The Integrated Database for Labour Market Research
Parental long-term unemployment
The Danish National Prescription Registry
Parental alcohol abuse
Parental drug abuse
The Register of Support for Children and Adolescents
Foster care
The Population Education Register
Parental education
The Income Statistics Register
Family poverty (1987 onwards)

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Cohort Profile: The DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980

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Cohort Profile: The DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980

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ABSTRACT

Purpose:

The DANLIFE cohort is a prospective register-based study set up to investigate the complex life course mechanisms linking childhood adversities to health and well-being in childhood, adolescence and young adulthood including cumulative and synergistic actions and potentially sensitive periods in relation to health outcomes.

Participants:

All children born in Denmark in 1980 or thereafter have successively been included in the cohort totalling more than 2.2 million children. To date, the study population has been followed annually in the nationwide Danish registers for an average of 16.8 years with full data coverage in the entire follow-up period. The information is currently updated until 2015.

Findings to date:

DANLIFE provides information on a wide range of family-related childhood adversities (e.g. parental separation, death of a parent or sibling, economic disadvantage) with important psychosocial implications for health and well-being in childhood, adolescence and young adulthood. Measurement of covariates indicating demographic (e.g. age, gender), social (e.g., parental education) and health-related factors (e.g. birth weight) have also been included from the nationwide registers. In this cohort profile we provide an overview of the childhood adversities and covariates included in DANLIFE. We also demonstrate that there is a clear social gradient in the exposure to childhood adversities confirming clustering of adverse experiences within individuals.

Future plans:

The DANLIFE cohort provides a valuable platform for research into early life adversity and opens unique possibilities for testing new research ideas on how childhood adversities affect health across the life course.

Strengths and limitations of this study

- DANLIFE provides an unselected data source for investigation of the effects of a wide range of objectively measured childhood adversities on health outcomes in childhood, adolescence and young adulthood.
- The large sample size including all children born in Denmark in 1980 or thereafter have successively been included in the cohort totalling more than 2.2 million children to latest update in 2015, allows for the assessment of new research ideas addressing rare outcomes and complex mechanisms such as cumulative and synergistic actions and potential sensitive periods.
- The unique identification number given to all Danish residents enables linkage of information from any Danish register or existing (non-register based) cohort study to DANLIFE, providing opportunities to answer a wide range of research questions.
- The measures of childhood adversities and health-related outcomes in DANLIFE are solely register-based and may be vulnerable to misclassification.

INTRODUCTION

The fact that many adulthood diseases have roots in earlier life is by now quite well documented and hardly debatable. The life course approach to studying health, which has increasingly been gaining attention in the past two decades, acknowledges the long-term biological, psychosocial and behavioural processes that operate across the life span, linking earlier life exposures to health in later life.[1] These processes are extremely complex and far from being fully elucidated, but a growing amount of evidence suggests that in early life, when the brain and the physiological systems are not fully mature, exposure to psychosocial adversities may be particularly detrimental for future health and developmental trajectories. Advances in neuroscience, molecular biology, and epigenetics have put forward an intriguing hypothesis that adverse events experienced early in life, when the human stress response system is still under development, may produce long-lasting alterations in the way the brain and the body respond to stress.[2,3] These alterations, which can be traced not only on the behavioural, but also on the epigenetic level,[4] are, on one hand, an adaptation to a stressful environment; on the other hand, they may have long-lasting costs to future mental health and the normal regulation of the metabolic and cardiovascular systems, leading to physical health consequences.[5]

Given that childhood may constitute a sensitive period for a whole range of exposures, including the exposure to stress, the timing of these exposures is central to life course epidemiology. Furthermore, researchers in child development have long argued that while exposure to a single risk factor hardly ever causes enduring harm, experience of multiple risk factors often has consequences for health.[6,7] Thus, research of adversity needs to account for the accumulation of stressors from different domains as well and across the life span.[8,9] The empirical testing of the hypotheses regarding the exact timing of exposures as well as the cumulative and interactive effects of stressors requires large data materials with frequent repeated measures over time. The DANLIFE cohort is a large-scale repeated-measure dataset established to provide information on how childhood adversities affect health across the life course.

There exist a number of birth cohorts and other longitudinal studies with rich repeated information, which provide a valuable platform for life-course research on early life adversities and health.[10–13] The DANLIFE cohort is different from the existing datasets in several key ways and thus provides new opportunities within this research area. The DANLIFE cohort utilizes data from nationwide registers covering all children born in Denmark since 1980. Because the data is exclusively register-based, the DANLIFE sample is unselected, thus solving the problem of selection bias that observational studies are prone to. Furthermore, using the national registers ensures a very large sample size. The population covered by DANLIFE totals more than 2.2 million children. Thus the cohort provides strong statistical power needed to test hypotheses involving complex interactions.

Using register-only information has its limitation in that the psychosocial measures available are not very detailed. However, as we explain below, due to a unique civil registration system available in Denmark, it is also possible to link DANLIFE to other existing (non-register-based) studies of Danish participants or invite DANLIFE participants for more assessments. All register-based data on major life events, social adversity and health outcomes are routinely collected and continuously updated for all children included in the cohort. The precise recording of timing of the information in DANLIFE enables the assessment of temporality between exposures, outcomes and covariates as well as identification of potential critical and sensitive periods of exposure to childhood adversities. The cohort was specifically set up to test hypotheses on complex life course mechanisms including:

a) Investigating whether specific childhood adversities act independently, cumulatively or synergistically on clinical health outcomes across life stages.

b) Identifying potentially sensitive periods (e.g. infancy, childhood, adolescence, early adulthood) for childhood adversities in relation to health outcomes.

The DANLIFE cohort is placed at a secure server at *Statistics Denmark*. Access to Danish administrative and health registers is granted by *Statistics Denmark* and *The Danish Health Data Authorities*. Data is provided for research purposes in an anonymous and secure form.

COHORT DESCRIPTION

Study population

All children born in Denmark in 1980 or thereafter to mothers who had a civil personal registration (CPR) number at the time of birth have been identified in the Danish Civil Registration System (CRS)[14] and have successively been included in DANLIFE. The CPR number is a unique 10-digit number all Danish residents are given at birth or upon immigration, as are non-resident persons who become members of the Danish Labour Market Supplementary Pension Fund or pay taxes in Denmark.[14] The CPR-number permits exact linkage on individual level between national administrative, clinical, and health research registries in Denmark[14] and thus provides an opportunity for country-wide population-based studies on public health matters by covering information such as drug prescriptions, hospitalisations, income and employment[15] (Figure 1). Some register-based information can have missing data, e.g. immigrated parents of children who completed their education abroad will have missing data on education. Since the data from CRS provided to DANLIFE is updated annually and includes the population on the 1st of January each year, children who are live-born but die or emigrate within the same calendar year are not included in the data from CRS. Children who died or emigrated in their first year of life were instead identified in the Medical Birth Registry (MBR)[16] (n=13,756). In the period 1980-1996, MBR included all children born in Denmark to mothers with residency in Denmark at the time of birth. Since 1997, MBR includes all births taking place in Denmark by mothers who already have a CPR-number.[14,16] Immigrants not born in Denmark are not included in the DANLIFE cohort because no information on childhood adversities is available for immigrants prior to immigration. Valid and continuously updated information on many socioeconomic, demographic, and health-related factors from the Danish nationwide registers were provided by Statistics Denmark and the Danish Health Data Authorities to DANLIFE.

The study participants have been followed until emigration, death or the end of follow-up. The information is currently updated until the 31st of December 2015, but we will continue with annual

updates when the data becomes available. The current version of DANLIFE cohort includes 2,223,927 individuals followed for an average of 16.8 years corresponding to more than 37 million person-years (Figure 2). Individuals emigrating during follow-up (n=164,348; 7.4%) are censored at the date of emigration and are not re-entered into the cohort if ever returning to Denmark, since there would be an information gap in the period the person spent outside of Denmark. Censoring on date of death was possible using information from CRS (n=20,514; 0.9%).

Patient and Public Involvement

Patients or public were not involved in the design of this register-based cohort. Studies based on Danish registers do not require informed consent or involvement by the population nor is an ethical approval by the Danish National Committee on Health Research Ethics required.

Family linkage

The CPR-numbers of the parents in DANLIFE have been retrieved from the child's first year of life from CRS supplemented by information from MBR. The parents registered in CRS are the legal parents and biological parents can therefore not be distinguished from adoptive parents.[14] However, the number of children who are born in Denmark and adopted is approximately 1%.[17] The parents registered in MBR are assumed to be the biological parents.[16] The CPR-numbers of the parents were used to identify siblings as persons linked to the same mother and father and to identify twins as persons born to the same mother on the same day (+/- 1 day). The CPR-number of the parents can also be used to identify siblings who only share one parent. The linkage to parents and siblings in DANLIFE enable identification of exposure to a range of family-related childhood adversities, such as severe illness in the family. The family linkage also enables identification of family history of specific diseases through linkage to the Danish National Patient Registry.[18] Children with missing information on both parents in both CRS and MBR were not included in the DANLIFE cohort (n=3103), since it would be impossible to identify the siblings of these children as well as the exposure to most of the family-related childhood adversities.

Follow-up

The registers combined in DANLIFE are updated for research purposes once a year (Figure 1). Information comes from 9 registers: The Danish Civil Registration systems captures sex, date of birth, date of death, family identifier, emigration, nationality and parental separation[19], the Danish Medical Birth Register captures birth-related information[16,20], The Integrated Database for Labour Marked Research captures parental long-term unemployment[21], the Register of Support for Children and Adolescents captures foster care, the Income Statistics Register captures family poverty (only from 1987 and onwards)[22], The Population Education Register captures parental education[23], The Danish National Prescription Registry captures drug prescriptions[24], which we use to identify parental alcohol and drug abuse, The Danish Psychiatric Central Research Register captures admissions due to psychiatric diagnoses[25], which we use to identify parental and sibling psychiatric illness and parental alcohol and drug abuse, and the Danish National Patient Register captures hospital admissions with diagnose codes[18], which we use to identify parental and sibling somatic illness and parental alcohol and drug abuse.

To date, the DANLIFE cohort includes information from the 1st of January 1980 until the 31st of December 2015, and will continue to be updated as children are born and registered. The continuity of the Danish registries provides full data coverage in the entire follow-up period, except for information on family poverty, which is based on the household equivalised disposable income, which was only available from 1987 onwards. Most factors have been specified with an exact date such as date of birth, emigration, death, highest attained education and all somatic and psychiatric diagnoses registered in the National Patient Registry.[18] Information on personal income and transfer payments[22], labour market affiliation[21] and parental separation[14] are registered across a given calendar year and the timing of these adversities is therefore set to the year of occurrence (Table 1). Since the objective of the DANLIFE cohort is to enable assessment of the effects of adversities

experienced in childhood on health and well-being, we restricted the exposure period to 0-18 years of age. The exposure period can easily be altered to accommodate research projects with alternative objectives.

Childhood adversities and covariates

The uniqueness of DANLIFE lies within the definition and construction (e.g. death of a siblings needs to be constructed using a family identifier) of measures of selected childhood adversities with important psychosocial implications for health and well-being in childhood, adolescence and young adulthood. In childhood, the family environment plays a crucial role for development and well-being. At the same time, a straining family environment, and the social circumstances in which it takes place, may be major sources of stress in children.[8,26–29] Two aspects of family environment that have been shown to be important sources of stress in children are lack of responsive caregiving[2,30,31] and loss, or the threat of loss, within the family.[29,31–33] Social disadvantage in the family is also a source of stress in children as it may affect parenting skills and family climate, as well as the availability of social and material resources, such as high quality housing, proximity of good schools and recreation areas, etc.[34–36] The linkage between child, parents and siblings in DANLIFE enables measurement of a range of childhood adversities that are likely to affect the quality of caregiving (i.e. being placed in foster care, parental psychiatric illness, sibling psychiatric illness, and parental alcohol or drug abuse); indicate loss, or the threat of loss, within the family (i.e. parental somatic illness, sibling somatic illness, parental separation, and death of a parent or a sibling) and social disadvantage (i.e. family poverty and parental long-term unemployment). Table 1 provides an overview of the adversities included DANLIFE.

Table 1 Definition and timing of the childhood adversities included in the DANLIFE cohort

Adversity	Definition	Date
Foster care	Being placed in out-of-home care	Date of placement
Parental psychiatric illness	A parent's admission for at least one day with an ICD-8 or ICD-10 code related to psychiatric illness. ICD-8 codes: Psychoses (290-299 except 291); Neuroses, personality disorders and other nonpsychotic mental disorders (300-309 except 303-304); and Mental retardation (310-315); ICD-10 codes: Mental, behavioural and neurodevelopmental disorders (F00-F99 except F10-F19)	Date of diagnosis
Parental somatic illness	A parent diagnosed with one of the ICD-8 codes included in the Charlson comorbidity index[37] in the period 1980-1993 or the ICD-10 codes included in the updated version of the Charlson comorbidity index[38] in the period 1994-2015	Date of diagnosis
Parental death	Death of a parent	Date of death
Sibling psychiatric illness	A sibling's admission for at least one day with an ICD-8 or ICD-10 code related to psychiatric illness. ICD8 codes: Psychoses (290-299); Neuroses, personality disorders and other nonpsychotic mental disorders (300-309); and Mental retardation (310-315); ICD10 codes: Mental, behavioural and neurodevelopmental disorders (F00-F99)	Date of diagnosis
Sibling somatic illness	A sibling diagnosed with one of the following somatic illnesses related to mortality in children aged 0-18 years (ICD-8/ICD-10 codes): Malignant neoplasm (140-199/C00-C96); Congenital anomalies of the heart and circulatory system (746-747/Q20-Q28); Congenital anomalies of the nervous system (743/Q00-Q07); Cerebral palsy (343-344/G80-G83); Epilepsy (345/G40-G41); Cardiomyopathy (425/I42-I43); Congenital disorders of lipid metabolism (272/E75)	Date of diagnosis
Sibling death	Death of a sibling	Date of death
Parental alcohol abuse	A parent diagnosed with an illness related to alcohol abuse or receiving a prescription of a drug used in treatment of alcohol addiction. ICD-8 codes: Alcoholic psychosis (291); Alcoholism (303); Alcoholic cirrhosis of the liver (571.09); Alcoholic steatosis of the liver (571.10); ICD-10 codes: Alcohol psychosis and abuse syndrome (F10); Alcoholic polyneuropathy (G62.1); Alcoholic cardiomyopathy (I42.6); Alcoholic-induced acute (K85.2) and chronic (K86.0) pancreatitis; Alcoholic liver disease (K70); Alcoholic gastritis (K29.2); ATC codes: Drugs used in alcohol dependence (N07BB)	Date of diagnosis/ prescription
Parental drug abuse	A parent diagnosed with an illness related to drug abuse or receiving a prescription of a drug used in treatment of drug addiction. ICD-8 codes: Drug dependence (304); ICD-10 codes: Opioids (F11); Cannabinoids (F12); Sedatives/hypnotics (F13); Cocaine (F14); Other stimulants (F15); Hallucinogens (F16); Other and multiple drugs (F18-F19); ATC codes: Drugs used in opioid dependence (N07BC)	Date of diagnosis/ prescription
Parental separation	Separation of the parents	Year of separation
Parental long-term unemployment	A parent being unemployed for at least 12 months within two consecutive years	First year of unemployment
Poverty	Family income below 50% of the median national family income in a given year, in three consecutive years	Third consecutive year of poverty

An important and growing field within the life course framework is the assessment of mediation and interaction.[1] The following covariates for confounding, mediation and interaction assessment have been incorporated in DANLIFE so far: sex (*male*, *female*), age at any given time (based on date of birth), birth order, birth weight (in grams), parental age at any given time (based on date of birth),

ethnicity (*Danish, non-Danish* if at least one parent has a nationality other than Danish) and parental highest attained education at the time of birth (*low* ≤ 9 years i.e. mandatory education in Denmark; *middle* 10-12 years i.e. youth education and vocational education; and *high* >12 years). In Denmark, <9 years of schooling is equivalent to basic education mandatory by law, 10-12 years of schooling is equivalent to high school in the USA, and >12 years of schooling is any additional schooling (e.g. university). The definitions of the covariates can be altered to accommodate specific research objectives. In principle, the CPR-number enables the inclusion of information on exposures, outcomes and covariates from any Danish register or any other study on Danish participants, which has recorded CPR numbers, into the DANLIFE cohort given granted permission from the authorities responsible for data security. An overview of the nationwide registers that have been linked in the DANLIFE cohort and which specific adversities and covariates each register has provided information on is shown in Figure 1. Information from several registers has been combined to define the adversities representing parental alcohol and drug abuse (Table 1 and Figure 1).

FINDINGS TO DATE

DANLIFE is a newly established dataset and no results based on its data have therefore been published to date but several studies investigating the effect of childhood adversities on health outcomes such as cardiovascular disease, type 1 diabetes and all-cause mortality are ongoing. Here we present findings regarding the prevalence of adversities among Danes and the social gradient in the exposure to adversities. These findings are summarized in Table 2. Table 2 gives an overview of the exposure to the specific childhood adversities in the total study population of more than 2.2 million children. Parental separation was the most frequently experienced adversity during follow-up (29%) followed by parental long-term unemployment (25%). In this large study population, several thousand had experienced even the rarest adversities (i.e. sibling death and sibling psychiatric illness). Table 2 further shows a clear social gradient in the exposure to childhood adversities in the DANLIFE cohort. The proportions of children exposed to the specific childhood adversities are consistently increasing with decreasing levels of maternal education measured at the time of birth.

The gradient is strong for the adversities reflecting family poverty, parental unemployment, and parental alcohol and drug abuse. The social gradient is also pronounced for parental separation where as many as 40% of the children born to mothers with a low level of education have experienced separation compared with only 19% of the children born to mothers with a high level of education. The social gradient is evident for all childhood adversities included in the cohort.

Table 2 Exposure to specific childhood adversities according to maternal educational level

			Maternal education[a],[b]					
	Total		High		Middle		Low	
Adversity	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**2,223,927**	**100.0%**	**714,718**	**32.1%**	**869,775**	**39.1%**	**571,161**	**25.7%**
Foster care	66,069	3.0%	4,120	0.6%	13,087	1.5%	45,936	8.0%
Parental psychiatric illness	89,014	4.0%	15,501	2.2%	30,072	3.5%	40,953	7.2%
Parental somatic illness	270,529	12.2%	71,529	10.0%	103,317	11.9%	89,314	15.6%
Parental death	55,759	2.5%	11,605	1.6%	19,083	2.2%	23,453	4.1%
Sibling psychiatric illness	18,213	0.8%	4,133	0.6%	6,287	0.7%	7,294	1.3%
Sibling somatic illness	56,911	2.6%	15,793	2.2%	22,170	2.5%	17,694	3.1%
Sibling death	10,543	0.5%	2,516	0.4%	4,001	0.5%	3,679	0.6%
Parental alcohol abuse	146,186	6.6%	22,798	3.2%	49,422	5.7%	70,640	12.4%
Parental drug abuse	40,248	1.8%	4,707	0.7%	11,622	1.3%	22,694	4.0%
Parental separation	638,879	28.7%	136,615	19.1%	259,465	29.8%	230,359	40.3%
Parental long-term unemployment	558,534	25.1%	80,636	11.3%	201,602	23.2%	259,686	45.5%
Family poverty[c]	99,457	5.4%	13,655	1.9%	34,421	4.0%	46,338	8.1%

We used strata by maternal education as the majority of Danish children live with their mother (85%)[39]

[a]Missing information on maternal education, n=68,273 (3.1%). Immigrated women who completed their education abroad will have missing on education.

[b]High: >12 years; Middle: 10-12 years; Low: ≤9 years

[c]From 1987 onwards, total n=1,846,564

The accumulation of childhood adversities in the DANLIFE cohort is presented in Table 3. Almost half of the study population did not experience any childhood adversities during follow-up and almost 10% had experienced three or more adversities. The previously mentioned well-known clustering of social disadvantage can also be seen in Table 3. More than 60% of the children born to mothers with a high level of education at the time of birth have not experienced any adversities during follow-up compared with only 25% of the children born to mothers with a low level of education. Accordingly, only 3.5% of the children born to highly educated mothers have experienced three or more

adversities compared with 20% of the children born to mothers with a low educational level. This is also reflected in the average numbers of adversities experienced during follow-up among children born to mothers with a high (0.5), middle (0.9) and low (1.5) level of education.

Table 3 Accumulation of childhood adversities according to maternal educational level

			Maternal education[a,b]					
	Total		High		Middle		Low	
Adversities	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0	1,035,594	46.6%	449,025	62.8%	400,264	46.0%	147,138	25.8%
1	651,608	29.3%	181,006	25.3%	276,572	31.8%	179,500	31.4%
2	324,057	14.6%	59,621	8.3%	127,221	14.6%	129,297	22.6%
3+	212,668	9.6%	25,066	3.5%	65,718	7.6%	115,266	20.2%
Total	**2,223,927**	**100.0%**	**714,718**	**32.1%**	**869,755**	**39.1%**	**571,161**	**25.7%**
Mean no. adversities			0.5		0.9		1.5	

We used strata by maternal education as the majority of Danish children live with their mother (85%)[39]

[a]Missing information on maternal education, n=68,273 (3.1%). Immigrated women who completed their education abroad will have missing on education.

[b]High: >12 years; Middle: 10-12 years; Low: ≤9 years

STRENGTHS AND LIMITATIONS

The main strengths of DANLIFE include the unselected sample and the large sample size. The unselected sample ensures unbiased estimates of the effects of adversity on clinical outcomes, and the large sample size and linkage to medical registers give the possibility to study very rare health outcomes, including possibilities for interaction analyses, which tend to require a lot of statistical power. Yearly updated information provides higher time resolution than most available birth cohorts and allows for estimation of exposure trajectories (i.e. moving in and out of poverty) and rather precise timing of exposures, which is crucial for investigation of critical and sensitive periods. Finally, information about exposures and outcomes that comes from registers is more objective than questionnaire-based data, as they are not subject to recall bias and other type of biases that are associated with self-reporting (e.g. participants' personality affecting their over-reporting of symptoms).[40]

The DANLIFE sample is still very young, with a maximum age of 36 years, and therefore quite healthy. Even though many diseases will not be manifested until a later age, we still observe more than 20,000 deaths and a considerable number of clinical outcomes such as cardiovascular disease, type 1 diabetes and sub-types of cancer in the DANLIFE sample. Thus, the large sample size provides a unique opportunity to evaluate effects of childhood adversities on clinical health outcomes in early adult life, which is a severely understudied area due to lack of statistical power and few cases in previous life course studies.

On the other hand, defining exposures and outcomes based on registers has important trade-offs. With respect to outcomes, only clinical diagnoses are available for investigation. This for example means that only severe mental health problems resulting in hospital admission will be captured in the data. Similarly, many relevant exposures related to family dynamics and sensitive care cannot be measured using registers. Furthermore, those measures that can be defined via registers are crude and may be vulnerable to misclassification. To illustrate, the effects of parental separation on children's well-being may be modified by a large number of circumstances, such as the extent to which parents are able to collaborate post-divorce and the shared custody arrangement. It may also be important whether parents enter new relationships once their marriage is dissolved. This information can only to a very limited degree be obtained via registers. As an example of possible misclassification, parental psychiatric illness, which may be severe enough to affect the family functioning, but not severe enough to result in hospitalization, will not be captured in registers.

However, the limitations concerning crude or incomplete measures can be overcome if DANLIFE data are combined with more precise questionnaire based measures: because the CPR-number is available for all participants, it is possible to link DANLIFE to other, non-register-based cohort studies of Danish participants or to invite a sub-sample of those who are in the DANLIFE cohort for a more

detailed assessment. Thus, the DANLIFE cohort provides a valuable platform for research into early life adversity and opens a lot of unique possibilities for testing new research ideas.

COLLABORATION

Access to the Danish register data must be granted by Statistics Denmark and The Danish Health Data Authorities and is therefore not open access. Access to the established DANLIFE cohort is available to other investigators through collaborative agreements and a secured access. Please contact Professor Naja Hulvej Rod [nahuro@sund.ku.dk] for further information.

FURTHER DETAILS

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Author statement

JB, ND, NHR were involved in the conception and design of the study. JB and AR were responsible for data management and analyses. All authors contributed to the writing of the manuscript and have critically revised and approved the final version.

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Competing Interest

None declared.

Data availability statement

Access to DANLIFE is available through collaborative agreements and granted access to the Danish registers by Statistics Denmark and The Danish Health Data Authorities. Please contact Professor Naja Hulvej Rod [nahuro@sund.ku.dk] for further information.

Figure 1 Nationwide Danish registers linked on individual level in the DANLIFE cohort using the Civil Personal Registration (CPR) number and the information they provided to the cohort

Figure 2 Characteristics of the DANLIFE study population and follow-up period

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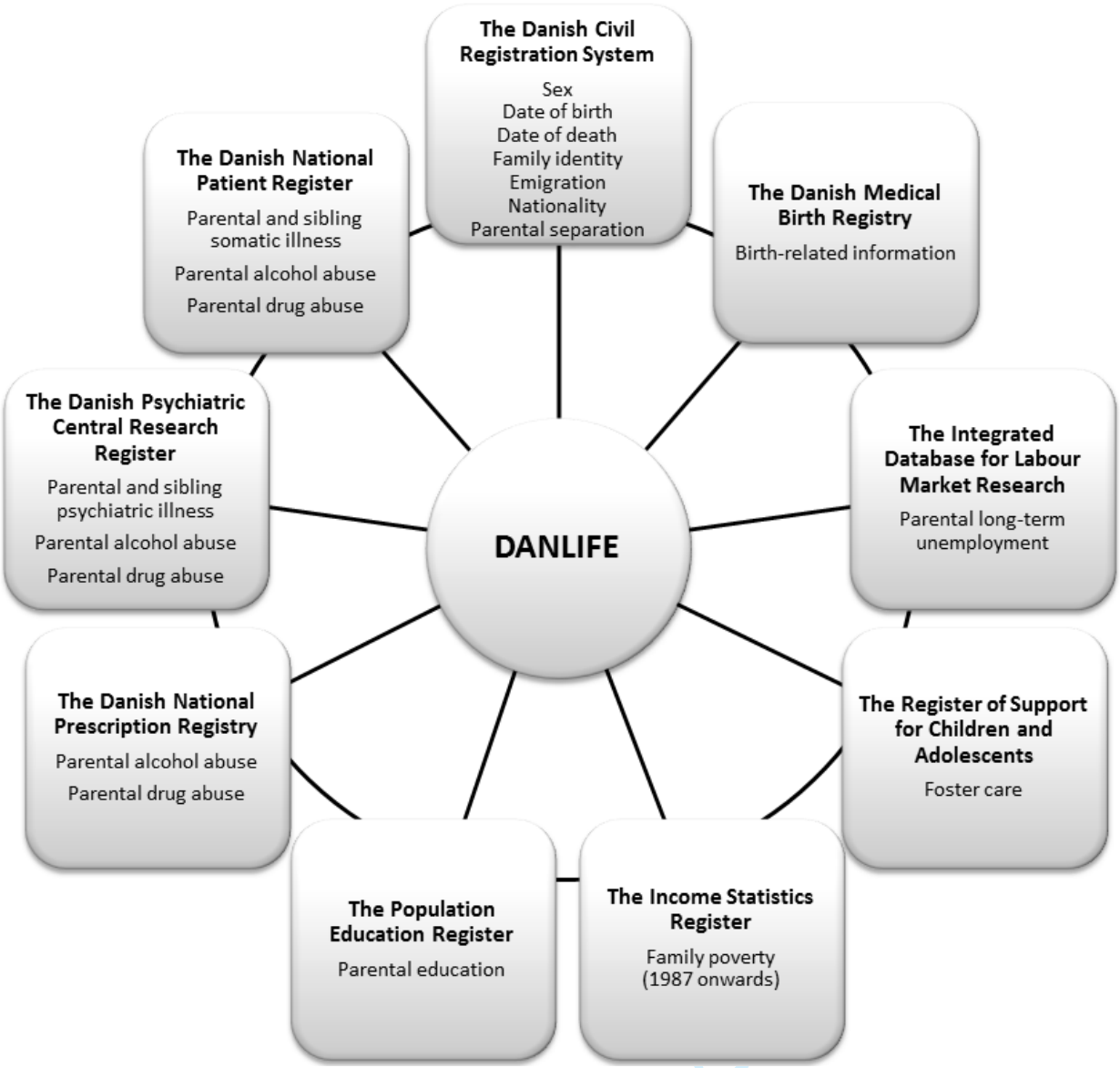
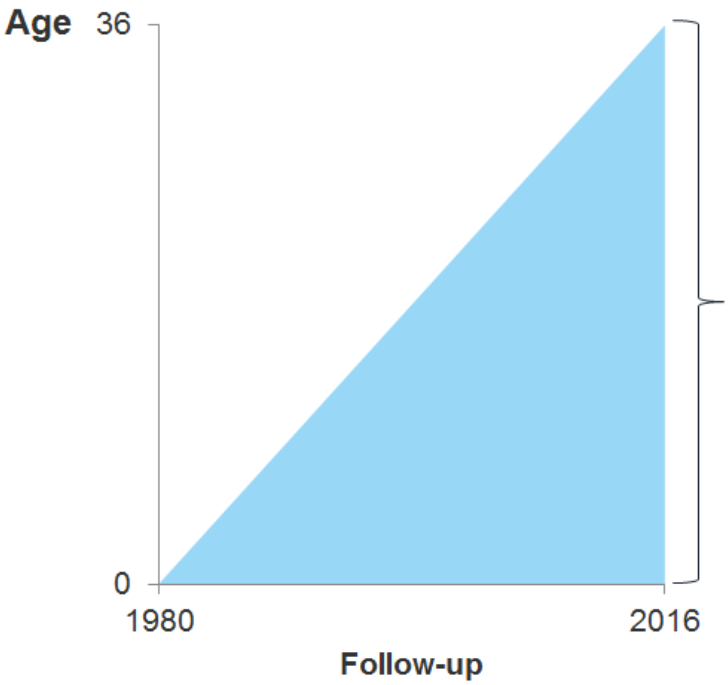

The Danish Civil Registration System
Sex
Date of birth
Date of death
Family identity
Emigration
Nationality
Parental separation
The Danish National Patient Register
Parental and sibling somatic illness
Parental alcohol abuse
Parental drug abuse
The Danish Medical Birth Registry
Birth-related information
The Danish Psychiatric Central Research Register
Parental and sibling psychiatric illness
Parental alcohol abuse
Parental drug abuse
DANLIFE
The Integrated Database for Labour Market Research
Parental long-term unemployment
The Danish National Prescription Registry
Parental alcohol abuse
Parental drug abuse
The Register of Support for Children and Adolescents
Foster care
The Population Education Register
Parental education
The Income Statistics Register
Family poverty (1987 onwards)

Study population: DANLIFE



Total N: 2,223,927

Deaths: 20,514 (0.9%)

Emigrations: 164,348 (7.4%)

Person years: 37.3 million

Mean follow-up: 16.8 years

Males: 51.3%

BMJ Open

Cohort Profile: The DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980

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Cohort Profile: The DANish LIFE course (DANLIFE) cohort, a prospective register-based cohort of all children born in Denmark since 1980

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ABSTRACT

Purpose:

The DANLIFE cohort is a prospective register-based study set up to investigate the complex life course mechanisms linking childhood adversities to health and well-being in childhood, adolescence and young adulthood including cumulative and synergistic actions and potentially sensitive periods in relation to health outcomes.

Participants:

All children born in Denmark in 1980 or thereafter have successively been included in the cohort totalling more than 2.2 million children. To date, the study population has been followed annually in the nationwide Danish registers for an average of 16.8 years with full data coverage in the entire follow-up period. The information is currently updated until 2015.

Findings to date:

DANLIFE provides information on a wide range of family-related childhood adversities (e.g. parental separation, death of a parent or sibling, economic disadvantage) with important psychosocial implications for health and well-being in childhood, adolescence and young adulthood. Measurement of covariates indicating demographic (e.g. age, gender), social (e.g., parental education) and health-related factors (e.g. birth weight) have also been included from the nationwide registers. In this cohort profile we provide an overview of the childhood adversities and covariates included in DANLIFE. We also demonstrate that there is a clear social gradient in the exposure to childhood adversities confirming clustering of adverse experiences within individuals.

Future plans:

The DANLIFE cohort provides a valuable platform for research into early life adversity and opens unique possibilities for testing new research ideas on how childhood adversities affect health across the life course.

Strengths and limitations of this study

- DANLIFE provides an unselected data source for investigation of the effects of a wide range of objectively measured childhood adversities on health outcomes in childhood, adolescence and young adulthood.
- DANLIFE includes all children born in Denmark in 1980 or thereafter totalling more than 2.2 million children in the latest update in 2015. Such population size allows for the assessment of new research ideas addressing rare outcomes and complex mechanisms such as cumulative and synergistic actions and potential sensitive periods.
- The unique identification number given to all Danish residents enables linkage of information from any Danish register or existing (non-register based) cohort study to DANLIFE, providing opportunities to answer a wide range of research questions.
- The measures of childhood adversities and health-related outcomes in DANLIFE are solely register-based and may be vulnerable to misclassification.

INTRODUCTION

The fact that many adulthood diseases have roots in earlier life is by now quite well documented and hardly debatable. The life course approach to studying health, which has increasingly been gaining attention in the past two decades, acknowledges the long-term biological, psychosocial and behavioural processes that operate across the life span, linking earlier life exposures to health in later life.[1] These processes are extremely complex and far from being fully elucidated, but a growing amount of evidence suggests that in early life, when the brain and the physiological systems are not fully mature, exposure to psychosocial adversities may be particularly detrimental for future health and developmental trajectories. Advances in neuroscience, molecular biology, and epigenetics have put forward an intriguing hypothesis that adverse events experienced early in life, when the human stress response system is still under development, may produce long-lasting alterations in the way the brain and the body respond to stress.[2,3] These alterations, which can be traced not only on the behavioural, but also on the epigenetic level,[4] are, on one hand, an adaptation to a stressful environment; on the other hand, they may have long-lasting costs to future mental health and the normal regulation of the metabolic and cardiovascular systems, leading to physical health consequences.[5]

Given that childhood may constitute a sensitive period for a whole range of exposures, including the exposure to stress, the timing of these exposures is central to life course epidemiology. Furthermore, researchers in child development have long argued that while exposure to a single risk factor hardly ever causes enduring harm, experience of multiple risk factors often has consequences for health.[6,7] Thus, research of adversity needs to account for the accumulation of stressors from different domains as well and across the life span.[8,9] The empirical testing of the hypotheses regarding the exact timing of exposures as well as the cumulative and interactive effects of stressors requires large data materials with frequent repeated measures over time. The DANLIFE cohort is a large-scale

repeated-measure dataset established to provide information on how childhood adversities affect health across the life course.

There exist a number of birth cohorts and other longitudinal studies with rich repeated information, which provide a valuable platform for life-course research on early life adversities and health.[10–13] The DANLIFE cohort is different from the existing datasets in several key ways and thus provides new opportunities within this research area. The DANLIFE cohort utilizes data from nationwide registers covering all children born in Denmark since 1980. Because the data is exclusively register-based, the DANLIFE sample is unselected, thus solving the problem of selection bias that observational studies are prone to. Furthermore, using the national registers ensures a very large sample size. The population covered by DANLIFE totals more than 2.2 million children. Thus the cohort provides strong statistical power needed to test hypotheses involving complex interactions.

Using register-only information has its limitation in that the psychosocial measures available are not very detailed. However, as we explain below, due to a unique civil registration system available in Denmark, it is also possible to link DANLIFE to other existing (non-register-based) studies of Danish participants or invite DANLIFE participants for more assessments. All register-based data on major life events, social adversity and health outcomes are routinely collected and continuously updated for all children included in the cohort. The precise recording of timing of the information in DANLIFE enables the assessment of temporality between exposures, outcomes and covariates as well as identification of potential critical and sensitive periods of exposure to childhood adversities. The cohort was specifically set up to test hypotheses on complex life course mechanisms including:

a) Investigating whether specific childhood adversities act independently, cumulatively or synergistically on clinical health outcomes across life stages.
b) Identifying potentially sensitive periods (e.g. infancy, childhood, adolescence, early adulthood) for childhood adversities in relation to health outcomes.

The DANLIFE cohort is placed at a secure server at *Statistics Denmark*. Access to Danish administrative and health registers is granted by *Statistics Denmark* and *The Danish Health Data Authorities*. Data is provided for research purposes in an anonymous and secure form.

COHORT DESCRIPTION

Study population

All children born in Denmark in 1980 or thereafter to mothers who had a civil personal registration (CPR) number at the time of birth have been identified in the Danish Civil Registration System (CRS)[14] and have successively been included in DANLIFE. The CPR number is a unique 10-digit number all Danish residents are given at birth or upon immigration, as are non-resident persons who become members of the Danish Labour Market Supplementary Pension Fund or pay taxes in Denmark.[14] The CPR-number permits exact linkage on individual level between national administrative, clinical, and health research registries in Denmark[14] and thus provides an opportunity for country-wide population-based studies on public health matters by covering information such as drug prescriptions, hospitalisations, income and employment[15] (Figure 1). Some register-based information can have missing data, e.g. immigrated parents of children who completed their education abroad will have missing data on education. Since the data from CRS provided to DANLIFE is updated annually and includes the population on the 1st of January each year, children who are live-born but die or emigrate within the same calendar year are not included in the data from CRS. Children who died or emigrated in their first year of life were instead identified in the Medical Birth Registry (MBR)[16] (n=13,756). In the period 1980-1996, MBR included all children born in Denmark to mothers with residency in Denmark at the time of birth. Since 1997, MBR includes all births taking place in Denmark by mothers who already have a CPR-number.[14,16] Immigrants not born in Denmark are not included in the DANLIFE cohort because no information on childhood adversities is available for immigrants prior to immigration. Valid and continuously updated information on many

socioeconomic, demographic, and health-related factors from the Danish nationwide registers were provided by Statistics Denmark and the Danish Health Data Authorities to DANLIFE.

The study participants have been followed until emigration, death or the end of follow-up. The information is currently updated until the 31st of December 2015, but we will continue with annual updates when the data becomes available. The current version of the DANLIFE cohort includes 2,223,927 individuals followed for an average of 16.8 years corresponding to more than 37 million person-years (Figure 2). Individuals emigrating during follow-up (n=164,348; 7.4%) are censored at the date of emigration and are not re-entered into the cohort if ever returning to Denmark, since there would be an information gap in the period the person spent outside of Denmark. Censoring on date of death was possible using information from CRS (n=20,514; 0.9%). Studies based on Danish registers do not require informed consent or involvement by the population nor is an ethical approval by the Danish National Committee on Health Research Ethics required.

Patient and public involvement

Patients or the public were not involved in the design of this register-based cohort.

Family linkage

The CPR-numbers of the parents in DANLIFE have been retrieved from the child's first year of life from CRS supplemented by information from MBR. The parents registered in CRS are the legal parents and biological parents can therefore not be distinguished from adoptive parents.[14] However, the number of children who are born in Denmark and adopted is approximately 1%.[17] The parents registered in MBR are assumed to be the biological parents.[16] The CPR-numbers of the parents were used to identify siblings as persons linked to the same mother and father and to identify twins as persons born to the same mother on the same day (+/- 1 day). The CPR-number of the parents can also be used to identify siblings who only share one parent. The linkage to parents and siblings in DANLIFE enable identification of exposure to a range of family-related childhood adversities, such as

severe illness in the family. The family linkage also enables identification of family history of specific diseases through linkage to the Danish National Patient Registry.[18] Children with missing information on both parents in both CRS and MBR were not included in the DANLIFE cohort (n=3103), since it would be impossible to identify the siblings of these children as well as the exposure to most of the family-related childhood adversities.

Data sources

The registers combined in DANLIFE are updated for research purposes once a year (Figure 1). Information comes from 9 registers: the Danish Civil Registration systems captures sex, date of birth, date of death, family identifier, emigration, nationality and parental separation[19], the Danish Medical Birth Register captures birth-related information[16,20], the Integrated Database for Labour Market Research captures parental long-term unemployment[21], the Register of Support for Children and Adolescents captures foster care, the Income Statistics Register captures family poverty (only from 1987 and onwards)[22], the Population Education Register captures parental education[23], the Danish National Prescription Registry captures drug prescriptions[24], which we use to identify parental alcohol and drug abuse, the Danish Psychiatric Central Research Register captures admissions due to psychiatric diagnoses[25], which we use to identify parental and sibling psychiatric illness and parental alcohol and drug abuse, and the Danish National Patient Register captures hospital admissions with diagnose codes[18], which we use to identify parental and sibling somatic illness and parental alcohol and drug abuse.

To date, the DANLIFE cohort includes information from the 1st of January 1980 until the 31st of December 2015, and will continue to be updated as children are born and registered. The continuity of the Danish registries provides full data coverage in the entire follow-up period, except for information on family poverty, which is based on the household equivalised disposable income, which was only available from 1987 onwards. Most factors have been specified with an exact date

such as date of birth, emigration, death, highest attained education and all somatic and psychiatric diagnoses registered in the National Patient Registry.[18] Information on personal income and transfer payments[22], labour market affiliation[21] and parental separation[14] are registered across a given calendar year and the timing of these adversities is therefore set to the year of occurrence (Table 1). Since the objective of the DANLIFE cohort is to enable assessment of the effects of adversities experienced in childhood on health and well-being, we restricted the exposure period to 0-18 years of age. The exposure period can easily be altered to accommodate research projects with alternative objectives.

Childhood adversities and covariates

The uniqueness of DANLIFE lies within the definition and construction (e.g. death of a siblings needs to be constructed using a family identifier) of measures of selected childhood adversities with important psychosocial implications for health and well-being in childhood, adolescence and young adulthood. In childhood, the family environment plays a crucial role for development and well-being. At the same time, a straining family environment, and the social circumstances in which it takes place, may be major sources of stress in children.[8,26–29] Two aspects of family environment that have been shown to be important sources of stress in children are instable family dynamics with lack of responsive caregiving[2,30,31] and loss or the threat of loss within the family.[29,31–33] Material deprivation in the family is also a source of stress in children as it may affect parenting skills and family climate, as well as the availability of social and material resources, such as high quality housing, proximity of good schools and recreation areas, etc.[34–36]The linkage between child, parents and siblings in DANLIFE enables measurement of a range of childhood adversities that are likely to affect the family dynamics and quality of caregiving (i.e. parental separation, being placed in foster care, parental psychiatric illness, sibling psychiatric illness, and parental alcohol or drug abuse); indicate loss, or the threat of loss, within the family (i.e. parental somatic illness, sibling somatic illness, and death of a parent or a sibling) and material deprivation (i.e. family poverty and parental long-term unemployment). Table 1 provides an overview of the adversities included DANLIFE.

Table 1 Definition and timing of the childhood adversities included in the DANLIFE cohort

Adversity	Definition	Date
Foster care	Being placed in out-of-home care	Date of placement
Parental psychiatric illness	A parent's admission for at least one day with an ICD-8 or ICD-10 code related to psychiatric illness. ICD-8 codes: Psychoses (290-299 except 291); Neuroses, personality disorders and other nonpsychotic mental disorders (300-309 except 303-304); and Mental retardation (310-315); ICD-10 codes: Mental, behavioural and neurodevelopmental disorders (F00-F99 except F10-F19)	Date of diagnosis
Parental somatic illness	A parent diagnosed with one of the ICD-8 codes included in the Charlson comorbidity index[37] in the period 1980-1993 or the ICD-10 codes included in the updated version of the Charlson comorbidity index[38] in the period 1994-2015	Date of diagnosis
Parental death	Death of a parent	Date of death
Sibling psychiatric illness	A sibling's admission for at least one day with an ICD-8 or ICD-10 code related to psychiatric illness. ICD8 codes: Psychoses (290-299); Neuroses, personality disorders and other nonpsychotic mental disorders (300-309); and Mental retardation (310-315); ICD10 codes: Mental, behavioural and neurodevelopmental disorders (F00-F99)	Date of diagnosis
Sibling somatic illness	A sibling diagnosed with one of the following somatic illnesses related to mortality in children aged 0-18 years (ICD-8/ICD-10 codes): Malignant neoplasm (140-199/C00-C96); Congenital anomalies of the heart and circulatory system (746-747/Q20-Q28); Congenital anomalies of the nervous system (743/Q00-Q07); Cerebral palsy (343-344/G80-G83); Epilepsy (345/G40-G41); Cardiomyopathy (425/I42-I43); Congenital disorders of lipid metabolism (272/E75)	Date of diagnosis
Sibling death	Death of a sibling	Date of death
Parental alcohol abuse	A parent diagnosed with an illness related to alcohol abuse or receiving a prescription of a drug used in treatment of alcohol addiction. ICD-8 codes: Alcoholic psychosis (291); Alcoholism (303); Alcoholic cirrhosis of the liver (571.09); Alcoholic steatosis of the liver (571.10); ICD-10 codes: Alcohol psychosis and abuse syndrome (F10); Alcoholic polyneuropathy (G62.1); Alcoholic cardiomyopathy (I42.6); Alcoholic-induced acute (K85.2) and chronic (K86.0) pancreatitis; Alcoholic liver disease (K70); Alcoholic gastritis (K29.2); ATC codes: Drugs used in alcohol dependence (N07BB)	Date of diagnosis/ prescription
Parental drug abuse	A parent diagnosed with an illness related to drug abuse or receiving a prescription of a drug used in treatment of drug addiction. ICD-8 codes: Drug dependence (304); ICD-10 codes: Opioids (F11); Cannabinoids (F12); Sedatives/hypnotics (F13); Cocaine (F14); Other stimulants (F15); Hallucinogens (F16); Other and multiple drugs (F18-F19); ATC codes: Drugs used in opioid dependence (N07BC)	Date of diagnosis/ prescription
Parental separation	Separation of the parents	Year of separation
Parental long-term unemployment	A parent being unemployed for at least 12 months within two consecutive years	First year of unemployment
Poverty	Family income below 50% of the median national family income in a given year, in three consecutive years	Third consecutive year of poverty

An important and growing field within the life course framework is the assessment of mediation and interaction.[1] The following covariates for confounding, mediation and interaction assessment have been incorporated in DANLIFE so far: sex (*male*, *female*), age at any given time (based on date of

birth), birth order, birth weight (in grams), parental age at any given time (based on date of birth), ethnicity (*Danish, non-Danish* if at least one parent has a nationality other than Danish) and parental highest attained education at the time of birth (*low* ≤ 9 years i.e. mandatory education in Denmark; *middle* 10-12 years i.e. youth education and vocational education; and *high* >12 years). In Denmark, <9 years of schooling is equivalent to basic education mandatory by law, 10-12 years of schooling is equivalent to high school in the USA, and >12 years of schooling is any additional schooling (e.g. university). The definitions of the covariates can be altered to accommodate specific research objectives. In principle, the CPR-number enables the inclusion of information on exposures, outcomes and covariates from any Danish register or any other study on Danish participants, which has recorded CPR numbers, into the DANLIFE cohort given granted permission from the authorities responsible for data security. An overview of the nationwide registers that have been linked in the DANLIFE cohort and which specific adversities and covariates each register has provided information on is shown in Figure 1. Information from several registers has been combined to define the adversities representing parental alcohol and drug abuse (Table 1 and Figure 1).

FINDINGS TO DATE

DANLIFE is a newly established dataset and no results based on its data have therefore been published to date but several studies investigating the effect of childhood adversities on health outcomes such as cardiovascular disease, type 1 diabetes and all-cause mortality are ongoing. Here we present findings regarding the prevalence of adversities among Danes and the social gradient in the exposure to adversities. These findings are summarized in Table 2. Table 2 gives an overview of the exposure to the specific childhood adversities in the total study population of more than 2.2 million children. Parental separation was the most frequently experienced adversity during follow-up (29%) followed by parental long-term unemployment (25%). In this large study population, several thousand had experienced even the rarest adversities (i.e. sibling death and sibling psychiatric illness). Table 2 further shows a clear social gradient in the exposure to childhood adversities in the

DANLIFE cohort. The proportions of children exposed to the specific childhood adversities are consistently increasing with decreasing levels of maternal education measured at the time of birth. The gradient is strong for the adversities reflecting family poverty, parental unemployment, and parental alcohol and drug abuse. The social gradient is also pronounced for parental separation where as many as 40% of the children born to mothers with a low level of education have experienced separation compared with only 19% of the children born to mothers with a high level of education. The social gradient is evident for all childhood adversities included in the cohort.

Table 2 Exposure to specific childhood adversities according to maternal educational level

			Maternal education[a],[b]					
	Total		High		Middle		Low	
Adversity	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**2,223,927**	**100.0%**	**714,718**	**32.1%**	**869,775**	**39.1%**	**571,161**	**25.7%**
Foster care	66,069	3.0%	4,120	0.6%	13,087	1.5%	45,936	8.0%
Parental psychiatric illness	89,014	4.0%	15,501	2.2%	30,072	3.5%	40,953	7.2%
Parental somatic illness	270,529	12.2%	71,529	10.0%	103,317	11.9%	89,314	15.6%
Parental death	55,759	2.5%	11,605	1.6%	19,083	2.2%	23,453	4.1%
Sibling psychiatric illness	18,213	0.8%	4,133	0.6%	6,287	0.7%	7,294	1.3%
Sibling somatic illness	56,911	2.6%	15,793	2.2%	22,170	2.5%	17,694	3.1%
Sibling death	10,543	0.5%	2,516	0.4%	4,001	0.5%	3,679	0.6%
Parental alcohol abuse	146,186	6.6%	22,798	3.2%	49,422	5.7%	70,640	12.4%
Parental drug abuse	40,248	1.8%	4,707	0.7%	11,622	1.3%	22,694	4.0%
Parental separation	638,879	28.7%	136,615	19.1%	259,465	29.8%	230,359	40.3%
Parental long-term unemployment	558,534	25.1%	80,636	11.3%	201,602	23.2%	259,686	45.5%
Family poverty[c]	99,457	5.4%	13,655	1.9%	34,421	4.0%	46,338	8.1%

We used strata by maternal education as the majority of Danish children live with their mother (85%)[39]

[a]Missing information on maternal education, n=68,273 (3.1%). Immigrated women who completed their education abroad will have missing on education.

[b]High: >12 years; Middle: 10-12 years; Low: ≤9 years

[c]From 1987 onwards, total n=1,846,564

The accumulation of childhood adversities in the DANLIFE cohort is presented in Table 3. Almost half of the study population did not experience any childhood adversities during follow-up and almost 10% had experienced three or more adversities. The previously mentioned well-known clustering of social disadvantage can also be seen in Table 3. More than 60% of the children born to mothers with

a high level of education at the time of birth have not experienced any adversities during follow-up compared with only 25% of the children born to mothers with a low level of education. Accordingly, only 3.5% of the children born to highly educated mothers have experienced three or more adversities compared with 20% of the children born to mothers with a low educational level. This is also reflected in the average numbers of adversities experienced during follow-up among children born to mothers with a high (0.5), middle (0.9) and low (1.5) level of education.

Table 3 Accumulation of childhood adversities according to maternal educational level

			Maternal education[a,b]					
	Total		High		Middle		Low	
Adversities	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Total	**2,223,927**	**100.0%**	**714,718**	**32.1%**	**869,755**	**39.1%**	**571,161**	**25.7%**
0	1,035,594	46.6%	449,025	62.8%	400,264	46.0%	147,138	25.8%
1	651,608	29.3%	181,006	25.3%	276,572	31.8%	179,500	31.4%
2	324,057	14.6%	59,621	8.3%	127,221	14.6%	129,297	22.6%
3+	212,668	9.6%	25,066	3.5%	65,718	7.6%	115,266	20.2%
Mean no. adversities			0.5		0.9		1.5	

We used strata by maternal education as the majority of Danish children live with their mother (85%)[39]

[a]Missing information on maternal education, n=68,273 (3.1%). Immigrated women who completed their education abroad will have missing on education.

[b]High: >12 years; Middle: 10-12 years; Low: ≤9 years

STRENGTHS AND LIMITATIONS

The main strengths of DANLIFE include the unselected sample and the large sample size. The unselected sample ensures unbiased estimates of the effects of adversity on clinical outcomes, and the large sample size and linkage to medical registers give the possibility to study very rare health outcomes, including possibilities for interaction analyses, which tend to require a lot of statistical power. Yearly updated information provides higher time resolution than most available birth cohorts and allows for estimation of exposure trajectories (i.e. moving in and out of poverty) and rather precise timing of exposures, which is crucial for investigation of critical and sensitive periods. Finally, information about exposures and outcomes that comes from registers is more objective than

questionnaire-based data, as they are not subject to recall bias and other type of biases that are associated with self-reporting (e.g. participants' personality affecting their over-reporting of symptoms).[40]

The DANLIFE sample is still very young, with a maximum age of 36 years, and therefore quite healthy. Even though many diseases will not be manifested until a later age, we still observe more than 20,000 deaths and a considerable number of clinical outcomes such as cardiovascular disease, type 1 diabetes and sub-types of cancer in the DANLIFE sample. Thus, the large sample size provides a unique opportunity to evaluate effects of childhood adversities on clinical health outcomes in early adult life, which is a severely understudied area due to lack of statistical power and few cases in previous life course studies.

On the other hand, defining exposures and outcomes based on registers has important trade-offs. With respect to outcomes, only clinical diagnoses are available for investigation. This for example means that only severe mental health problems resulting in hospital admission will be captured in the data. Similarly, many relevant exposures related to family dynamics and sensitive care cannot be measured using registers. Furthermore, those measures that can be defined via registers are crude and may be vulnerable to misclassification. To illustrate, the effects of parental separation on children's well-being may be modified by a large number of circumstances, such as the extent to which parents are able to collaborate post-divorce and the shared custody arrangement. It may also be important whether parents enter new relationships once their marriage is dissolved. This information can only to a very limited degree be obtained via registers. As an example of possible misclassification, parental psychiatric illness, which may be severe enough to affect the family functioning, but not severe enough to result in hospitalization, will not be captured in registers. However, the limitations concerning crude or incomplete measures can be overcome if DANLIFE data are combined with more precise questionnaire based measures: because the CPR-number is

available for all participants, it is possible to link DANLIFE to other, non-register-based cohort studies of Danish participants or to invite a sub-sample of those who are in the DANLIFE cohort for a more detailed assessment. Thus, the DANLIFE cohort provides a valuable platform for research into early life adversity and opens a lot of unique possibilities for testing new research ideas.

COLLABORATION

Access to the Danish register data must be granted by Statistics Denmark and The Danish Health Data Authorities and is therefore not open access. Access to the established DANLIFE cohort is available to other investigators through collaborative agreements and a secured access. Please contact Professor Naja Hulvej Rod [nahuro@sund.ku.dk] for further information.

FURTHER DETAILS

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Author statement

JB, ND, NHR were involved in the conception and design of the study. JB and AR were responsible for data management and analyses. All authors contributed to the writing of the manuscript and have critically revised and approved the final version.

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Competing Interest

None declared.

Data availability statement

Access to DANLIFE is available through collaborative agreements and granted access to the Danish registers by Statistics Denmark and The Danish Health Data Authorities. Please contact Professor Naja Hulvej Rod [nahuro@sund.ku.dk] for further information.

Figure 1 Nationwide Danish registers linked on individual level in the DANLIFE cohort using the Civil Personal Registration (CPR) number and the information they provided to the cohort

Figure 2 Characteristics of the DANLIFE study population and follow-up period

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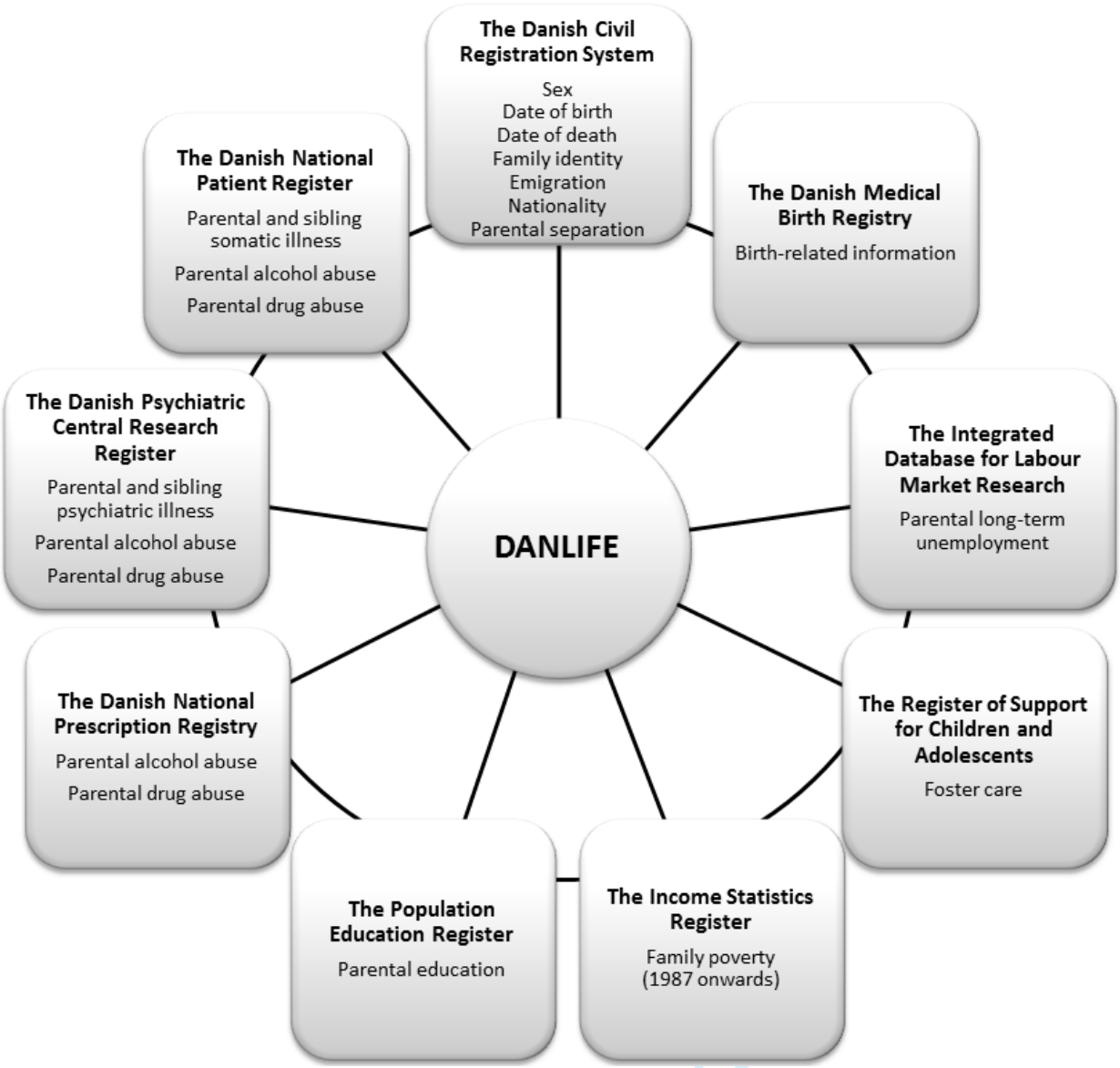
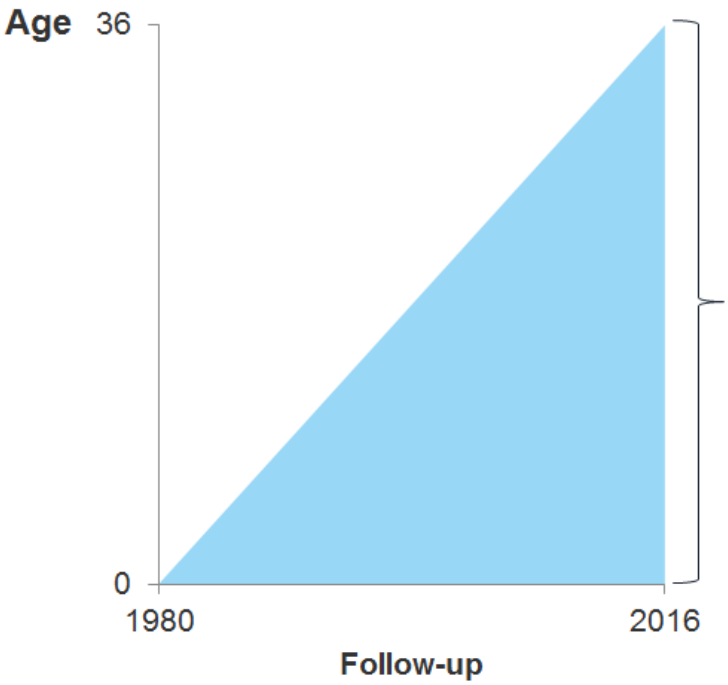

The Danish Civil Registration System
Sex
Date of birth
Date of death
Family identity
Emigration
Nationality
Parental separation
The Danish National Patient Register
Parental and sibling somatic illness
Parental alcohol abuse
Parental drug abuse
The Danish Medical Birth Registry
Birth-related information
The Danish Psychiatric Central Research Register
Parental and sibling psychiatric illness
Parental alcohol abuse
Parental drug abuse
DANLIFE
The Integrated Database for Labour Market Research
Parental long-term unemployment
The Danish National Prescription Registry
Parental alcohol abuse
Parental drug abuse
The Register of Support for Children and Adolescents
Foster care
The Population Education Register
Parental education
The Income Statistics Register
Family poverty (1987 onwards)

Study population: DANLIFE



Total N: 2,223,927

Deaths: 20,514 (0.9%)

Emigrations: 164,348 (7.4%)

Person years: 37.3 million

Mean follow-up: 16.8 years

Males: 51.3%