Contents

Nomenclature

Full cohort: The entire source population from which the iPSYCH2015 sample was selected (also sometimes referred to as the iPSYCH2015 study base).

Cases (or iPSYCH cases): Individuals fully sampled from the source population by 2012 (iPSYCH2012) and by 2015 being diagnosed with one of the focus disorders. Cases in iPSYCH2012 included individuals diagnosed one or more of the following disorders: autism spectrum disorder, attention-deficit/hyperactivity disorder, affective disorder (including bipolar disorder), and schizophrenia by 2012. Case groups in iPSYCH2015 included: autism spectrum disorder, attention-deficit/hyperactivity disorder, affective disorder, schizophrenia spectrum disorder, and postpartum psychiatric disorder. These disorders and nested disorders are also referred to as primary outcomes or primary phenotypes.

Subcohort: A smaller cohort randomly selected from the source population as part of the case-cohort design, to obtain population-representative controls in which the expensive exposure (genetic information in iPSYCH) can be measured. We distinguish between the two subcohorts (two random samples) selected in connection with the two selections in 2012 and 2015, respectively, and the combined subcohort, which is the union of the two random subcohorts and is referred to in short as *the subcohort*. Note that individuals from birth years 2006-2008 in the subcohort are underrepresented compared to those from birth years 1981-2005.

First phase selection (iPSYCH2012 case-cohort sample): The first selected case-cohort sample (n = 86,189) including all cases with specific psychiatric disorders by 2012 (n = 57,377) and a 2.037% (n = 30,000) randomly selected subcohort from the iPSYCH2012 source population, all born between 1981 and 2005.[1]

Second phase selection: The second phase selection including 57,377 cases (additionally schizophrenia spectrum disorder and postpartum psychiatric disorder) by 2015 and a 21,000 (1.267%) randomly selected subcohort from the full cohort, all born between 1981 and 2008. Note, in the subcohort, 385 individuals were already selected in 2012 and 2958 individuals were also selected as a case. The second phase selection has previously been referred to as *iPSYCH2015i*, but may be confused with the additional individuals not already genotyped in iPSYCH2012 [2].

iPSYCH sample (or iPSYCH2015 case-cohort sample): The combined sample of the two case-cohort samples including 141,265 individuals (88,372 cases and 50,615 subcohort members) [2].

Primary outcome: Disorder nested in the case groups in the iPSYCH sample. In the present study the following disorders were used as primary outcomes: affective disorder, schizophrenia, schizophrenia spectrum disorder, bipolar disorder, autism spectrum disorder, and attention-deficit/hyperactivity disorder. Note that we use the term *primary outcome* even when the disorder was first identified after 2015 but originally sampled as a different case or subcohort member. Also sometimes referred to as primary phenotype.

Secondary outcome: Any outcome (other than the iPSYCH primary outcomes) that can be identified in the existing samples. In the present study we used the following secondary outcomes: epilepsy, anxiety disorders, migraine, asthma, type 1 diabetes, injury, traumatic brain injury, substance use disorder, and death. Also sometimes referred to as secondary phenotype.

Initial selection probability: Probability of being selected into the first or second phase case-cohort samples (0.02037 and 0.01267, respectively). Cases in iPSYCH were all selected with probability 1.

Final inclusion probability: Probability of being included in the combined iPSYCH sample, stratified by two birth cohorts 1981-2005 and 2006-2008, or calculated as an average of the two inclusion probabilities based on full cohort numbers in each birth cohort. Cases in iPSYCH were all included with probability 1.

Supplementary note 1: The augmented case-cohort design

Notation

The augmented case-cohort design here refers to a two-phase sampling design where the original case-cohort sample is expanded with new cases and subcohort.

We adapt the notation from Petersen et al. [3] and Kulathinal et al. [4] with extension to a two-phase case-cohort sampling design to mimic the sampling design used in iPSYCH.

Let N denote the size of the full cohort. Let the index set $C = \{i = 1, \dots, N\}$ denote the full cohort including N individuals, $SC = \{i \in C : SC_i = 1\}$, where $SC_i = 1$ if individual i is selected into the (combined) subcohort, and $D = \{i \in C : D_i = 1\}$, where $D_i = 1$ if the individual i is a case. Similarly, $C1$ refer to the cohort at the time of the first phase selection, which is assumed to be nested in the augmented source cohort $C2$ for the second phase selection, the latter considered equal to the full cohort, i.e. $C2 = C$. The index sets $SC1$ and $SC2$ refer to the two randomly selected subcohorts selected from $C1$ and $C2$, respectively. The case-cohort sample is denoted by $R = SC \cup D$. The sets $C \backslash D$ and $SC \backslash D$ are index sets of the the non-cases in the full cohort and non-cases in the subcohort.

We denote the remaining sample sizes (of above-defined sets) by n (combined subcohort), n_d (cases), N_1 (phase 1 source population), $N_2 = N$ (phase 2 source population = the full cohort), n_1 (phase 1 subcohort) and n_2 (phase 2 subcohort), N^0(non-cases in the full cohort), and n^0 (non-cases in the subcohort).

The iPSYCH sample

The iPSYCH sample is an example of an augmented case-cohort design, where the subcohort was expanded by a second randomly selected subcohort and more cases were included (outcome definitions and extended follow-up). The full cohort, C, refers to the iPSYCH2015 source population (or study base); the entire Danish population of singletons born in Denmark May 1, 1981 to December 31, 2008, who had a known mother, were surviving and residing in Denmark on their first birthday (n= 1,657,449). The iPSYCH sample (or iPSYCH2015 sample), R, was formed by the two iPSYCH case-cohort samples, $R1$ and $R2$, selected in 2012 and 2015, respectively. The two selections are illustrated in a Lexis diagram in Supplementary Fig.1: 1) The iPSYCH2012 case-cohort sample, $R1$ (first selection) was drawn from the original source population, $C1$ $(N_1 = 1{,}472{,}762)$, born May 1, 1981 to December 31, 2005. This case-cohort sample consists of all cases diagnosed with disorders autism spectrum disorder, attention-deficit/hyperactivity disorder, affective disorder, and schizophrenia by December 31, 2012, and a randomly selected subcohort, $SC1$ $(n_1 = 30{,}000)$ [1]; 2) An augmented case-cohort sample (second selection, $R2$) was drawn from the augmented source population, born May 1, 1981 to December 31, 2008, and includes all cases with autism spectrum disorder, attention-deficit/hyperactivity disorder, affective disorder, schizophrenia spectrum disorder and postpartum psychiatric disorder (*all cases*, D_{all}), all diagnosed by December 31, 2015, and a new randomly selected subcohort, $SC2$, of $21{,}000$ individuals (with little overlap with the iPSYCH2012 subcohort). The sampling procedure has been described in detail elsewhere [1,2]. The entire iPSYCH sample, $R = R1 \cup R2 = SC1 \cup SC2 \cup D_{all}$, includes the union of the two subcohorts (with an intersection of 385

individuals) and above-mentioned cases in a combined subcohort of 50,615 (51,000 – 385) individuals and a total of 93,608 cases born 1981-2008 and diagnosed by 2015, of which 2958 are included in the random subcohort. The combined subcohort and all cases constitutes 3.1% and 5.6%, respectively, of the full cohort (N= 1,657,449).

Based on the sets described above, we considered the following study samples:

1) The full cohort, C, i.e. the entire iPSYCH source population
2) The subcohort (SC)
3) The subcohort and set of individuals with the disorder of interest ($SC\ U\ D$)
4) The entire iPSYCH sample ($R = SC \cup D_{all}$)

For 3) we varied the sample depending on the outcome of interest by 2015 for both primary outcomes, D, and secondary outcomes nested within the entire iPSYCH sample, $D = R \cap D_{full}$, where D_{full} denotes the (secondary) outcome in the full cohort by 2015. Consequently, the case-control status and corresponding weights differ for some individuals depending on outcomes included in the case sets. A visualization of the four sets can be found in Fig. 1 in the main paper.

Supplementary note 2: Inverse probability of sampling weights

Below we derive the birth cohort-specific inverse probability weights for the subcohort, where the probabilities refer to the probability of being included in the combined subcohort. These inclusion probabilities are based on the initial selection probabilities of the two subcohorts (simple random samples) from nested birth cohorts.

The initial selection probabilities for the subcohorts are given by

$$p(SC1_i = 1) = \frac{n_1}{N_1}$$

and

$$p(SC2_i = 1) = \frac{n_2}{N_2}$$

Because the first phase source population $C1$ is considered nested in the full cohort C, individuals in the combined subcohort may be considered a stratified sample formed by two mutually exclusive birth cohorts, $bc1$ and $bc2$. Thus we define the stratum-specific subcohorts as $SC^{s(bc1)} = \{i \in C: SC_i^{s(bc1)} = 1\}$ and as $SC^{s(bc2)} = \left\{i \in C: SC_i^{s(bc2)} = 1\right\}$, where *s(bc1)* and *s(bc1)* denotes the strata of the two birth cohorts.

Note that the sample was not stratified by design and thus individuals in the subcohort from the first birth cohort origins (was selected) from $C1 \cup C = C$ and not from $C1$ only.

Final birth cohort-specific inclusion probabilities can then be calculated from the above initial selection probabilities as

$$p\left(SC_i^{s(bc1)} = 1\right) = p(SC1_i = 1) + p(SC2_i = 1) - p(SC1_i = 1)p(SC2_i = 1)$$

$$= 1 - \big(1 - p(SC1_i = 1)\big)\big(1 - p(SC2_i = 1)\big)$$

$$p\big(SC_i^{s(bc2)} = 1\big) = p(SC2_i = 1)$$

Note that the above inclusion probability for the first birth cohort is slightly smaller than the sum of the two initial selection probabilities, because of the small probability of being selected twice, and that minor differences in source populations used in 2012 and 2015 were ignored.

The overall inclusion probability in the subcohort, considering the sample stratified by birth cohort, may be calculated as a weighted average across the two mutually exclusive birth cohorts:

$$p(SC_i = 1) = \; p\big(SC_i^{s(bc1)} = 1\big)\, p\big(C_i^{s(bc1)} = 1\big) + \; p\big(SC_i^{s(bc2)} = 1\big)\, p\big(C_i^{s(bc2)} = 1\big)$$

However, recall that the strata $s(bc1)$ and $s(bc2)$ were not well-defined for the full cohort, C, as these were not explicitly part of the sampling procedure.

Finally, inverse probability weights, w, were calculated as the birth cohort-specific inverse inclusion probabilities, in the spirit of Kalbfleisch and Lawless [5] as 1 for cases and the inverse of the inclusion probability for non-cases in the subcohort, i.e.

$$w_i^{s(k)} = \frac{1}{p\big(SC_i^{s(k)} = 1\big)}$$

Where the weights take different values depending on the birth cohort-specific stratum, $s(k),\ k \in \{bc1, bc2\}$.

The weights are then given by

$$w_i^{s(k)} = \begin{cases} 1 & if\ i \in D \\ \dfrac{1}{1 - \left(1 - \frac{n_1}{N_1}\right)\left(1 - \frac{n_2}{N_2}\right)} & if\ i \in SD \backslash D\ and\ k = bc1 \\ \dfrac{N_2}{n_2} & if\ i \in SD \backslash D\ and\ k = bc2 \end{cases}$$

Note, that the weights are based on the inclusion probability of the entire subcohort which for large samples, approximates the previously suggested weights, where cases are subtracted in both nominator and denominator ($w_i = N^0/n^0$) [5]. The approximation follows from the assumption that the proportion of cases in the subcohort (considered a simple random sample) equals the proportion of cases in the full cohort by, i.e. $\frac{\mathrm{n} - \mathrm{n}^0}{\mathrm{n}} = \frac{N - N^0}{N}$. This implies that $1 - \frac{n^0}{n} = 1 - \frac{N^0}{N}$, and thus $\frac{n^0}{N^0} = \frac{n}{N}$.

Selection and weights in iPSYCH

From the above formulas, and numbers in iPSYCH source population and selected subcohorts, we can calculate the initial selection probabilities and birth cohort-specific inclusion probabilities and

weights. Note that these probabilities were delineated at a common baseline for all outcomes of interest (age 1 year) and do not exactly mirror baseline for time at risk for a specific disorder.

Initial selection probabilities for the two phases of selection are

$$p(SC1_i = 1) = \frac{30{,}000}{1{,}472{,}762} = 0.02037$$

and

$$p(SC2_i = 1) = \frac{21{,}000}{1{,}657{,}449} = 0.01267$$

Final birth cohort-specific inclusion probabilities are then

$$p\left(SC_i^{b1981-2005} = 1\right) = 1 - (1 - 0.02037)(1 - 0.01267) = 0.03278$$
$$p\left(SC_i^{b2006-2008} = 1\right) = 0.01267$$

The overall (average) inclusion probability is

$$p(SC_i = 1) = 0.03278\frac{1{,}472{,}762}{1{,}657{,}449} + 0.01267\frac{184{,}687}{1{,}657{,}449} = 0.03054$$

The birth cohort-specific weights are then given by

$$w_i^{s(k)} = \begin{cases} 1 & if\ i \in D \\ \dfrac{1}{0.03278} = 30.5 & if\ i \in SD \backslash D\ and\ k = 1981 - 2005 \\ \dfrac{1}{0.01267} = 78.9 & if\ i \in SD \backslash D\ and\ k = 2006 - 2008 \end{cases}$$

Supplementary note 3: Population-based inference

The Cox regression model can be used to estimate incidence and incidence rate ratios. The incidence rates, or counting process of failures for individual i [6], can be written as

$$\lambda_i(t) = Y_i(t)\alpha_0(t)\exp\left(\beta_0^T Z_i(t)\right),$$

where $\alpha_0(t)$ is the baseline hazard function, β_0^T the vector of regression parameters corresponding to the $log(hazard\ ratio)$ for covariates, $Z_i(t)$, which may be time-dependet. $Y_i(t)$ denotes the risk indicator (1 if at risk, 0 otherwise) for individual i at time t.

In the full cohort, the incidence rate ratio (or hazard ratio) can be estimated from a Cox regression model by maximizing the partial likelihood,

$$L(\beta) = \prod_{t_j} \frac{\exp(\beta^T Z_{i_j}(t_j))}{\sum_{l \in C} Y_l(t_j) \exp(\beta^T Z_l(t_j))},$$

Where C is the set of all individuals in the full cohort, which reduces to those at risk at time t_j for $Y_l(t_j) = 1$.

In the setting of the case-cohort design, Z_i is only known for the cases and subcohort members, and we instead need to estimate β from the pseudo-likelihood, which approximates the partial likelihood function. The partial likelihood incorporates the weights and can be written as

$$L(\beta) = \prod_j \frac{Y_i(t_j) w_i(t_j) \exp(\beta^T Z_i(t_j))}{\sum_{l \in SC \cup D} Y_l(t_j) w_l(t_j) \exp(\beta^T Z_l(t_j))},$$

where $w_l(t_j)$ is the individual weight at time t_j, whereby the person-time is upweighted for non-case subcohort members. This partial likelihood is in line with the one suggested by Barlow in 1994 [7], and has earlier been presented by Self and Prentice in 1988 [8] as a partial likelihood splitting the denominator into cases and subcohort members, so the cases only contributed with a weight of 1 just before the time of event. Using the time-independent weights derived above, we set $w_l(t_j) = w_i^{s(k)}$, i.e. the weight for individual i only depend on the birth cohort-specific inclusion probabilities and not on the risk set at time t. This also means that we considered all individuals in the case-cohort sample at risk and thus contribute with person-time from baseline. A closed-form expression for the absolute risk,[6] along with robust standard error estimators,[7] and resampling empirical standard deviation[9] are readily available and implemented in R package survival adding + cluster(id) to the coxph() formula https://cran.r-project.org/web/packages/survival/vignettes/survival.pdf.

Supplementary Table 1 ICD-10 codes, age cutoffs, and counts for primary and secondary outcomes in iPSYCH2012, the entire iPSYCH sample and full cohort**.**

Sample			**iPSYCH 2012 (birth years 1981-2005)**		**The entire iPSYCH sample (birth years 1981-2008)**			**Full cohort (birth years 1981-2008)**	
				N		**N**		**N**	
Total sample				86189		141265		1657449	
Subcohort				30000		50615 (c)		NA	
Non-case subcohort				28812		47657		NA	
Primary outcomes (iPSYCH cases)	**ICD-10 code**	**min age**	**cal years**	**N (by 2012)**	**cal years**	**N (by 2015)**	**N (by 2021)**	**N (by 2015)**	**N (by 2021)**
Schizophrenia	F20	10	2009(b)-2012	3540	1994-2015	8113	9772	8113	13328
Schizophrenia Spectrum Disorder	F20-F29	10	NA	NA	1994-2015	16008	18644	16008	28721
Affective disorder	F30-F39	10	1994-2012	26380	1994-2015	40482	43519	40482	70175
Bipolar disorder (nested within affective disorder)	F30-F31	10	1994-2012	1928	1994-2015	3819	4868	3819	7696
Autism spectrum disorder	F84.0, F84.1, F84.5, F84.8, F84.9	1	1994-2012	16146	1994-2015	24975	26972	24975	40849
Attention-deficit/hyperactivity disorder	F90.0	1	1994-2012	18726	1994-2015	29668	31914	29668	45966
Postpartum psychiatric disorder	F00-F99 (a)	NA	NA	NA	1994-2015	3421	7052	3421	15336
Cases (outcomes in both iPSYCH2012 and iPSYCH2015)	F20, F30-F39, F84.0, F84.1, F84.5, F84.8, F84.9, F90.0	1 or 10	1994-2012	57377	1994-2015	88372	90678	88372	141505
Any case	All above	1 or 10	1994-2012	NA	1994-2015	93608	95351	93608	154498
Secondary outcomes of interest									
Epilepsy	G40	1	1994-2012	2849	1994-2015	4463	5039	24765	28840
Anxiety disorders	F40-48+F93	1	1994-2012	8491	1994-2015	17136	21543	36481	62261
Migraine	G43	1	1994-2012	1232	1994-2015	2500	3888	18239	30569
Asthma	J45-J46	1	1994-2012	6398	1994-2015	11156	12829	103548	119281
Type 1 diabetes	E10	1	1994-2012	554	1994-2015	959	1218	8148	10999

Injury	S00-T88	1	1994-2012	71382	1994-2015	119217	125167	1298845	1404835
Traumatic brain injury	S06.0 (mild), S06.1-S06.9 (severe), S02.0-S02.1, S02.7, S02.9 (skull fracture)	1	1994-2012	7870	1994-2015	13426	15745	107393	128867
Substance use disorder	F10-F19	10	1994-2012	9444	1994-2015	17710	21762	61537	85660
Death	Status from the Danish Civil Registration System	1	1982-2012	379	1982-2015	748	1411	7358	10240

(a) Psychiatric diagnosis within one year after giving birth to a live-born baby.

(b) Include all persons first diagnosed with Schizophrenia 2009-2012 and persons diagnosed before 2009 not already genotyped (GEMS 1+2, n=923).

(c) Including subcohorts selected in 2012 (n=30,000) and in 2015 (n = 21,000) with minor overlap (n=385).

SupplementaryTable 2 Weighted and unweighted counts, person-time at risk, events and overall incidence rates across different samples (full cohort, iPSYCH subcohort and case-cohort samples) for follow-up until 2015 and 2021.

Disorder	Sample	Number in sample	Weighted number	Person-years/1000	Weighted person-years /1000	Number of events [a]	Weighted number of events	Incidence rate /1000 person-years	Weighted incidence rate /1000 person-years
Follow-up until 2015									
Affective	Full cohort	1657449	1657449	31234.54	31234.54	38980	38980	1.25	1.2480
	Subcohort	50615	1659623.93	996.59	31267.18	1260	38435.87	1.26	1.2293
	Subcohort and outcome	89800	1660541.39	1768.90	31278.99	38980	38980	22.04	1.2462
	Subcohort and all cases	141265	1660674.91	2744.15	31286.12	38980	38980	14.20	1.2459
Epilepsy	Full cohort	1657449	1657449	30376.93	30376.93	24276	24276	0.80	0.7992
	Subcohort	50615	1659623.93	969.51	30420.98	803	25318.41	0.83	0.8323
	Subcohort and outcome	54258	1659629.53	1008.30	30421.72	4377	25402.53	4.34	0.8350
	Subcohort and all cases	141265	1660674.91	2843.24	30438.35	4377	25402.53	1.54	0.8346
Follow-up until 2021									
Affective	Full cohort	1657449	1657449	40160.92	40160.92	67118	67118	1.67	1.6712
	Subcohort	50615	1659623.93	1266.97	40205.02	2179	67147.56	1.72	1.6701
	Subcohort and outcome	89800	1660541.39	2039.90	40217.34	39824	67646.19	19.52	1.6820
	Subcohort and all cases	141265	1660674.91	3304.00	40223.43	41904	67376.4	12.68	1.6751
Epilepsy	Full cohort	1657449	1657449	39175.44	39175.44	28119	28119	0.72	0.7178
	Subcohort	50615	1659623.93	1236.49	39227.84	914	29140.22	0.74	0.7428
	Subcohort and outcome	54258	1659629.53	1275.28	39228.58	4488	29224.34	3.52	0.7450
	Subcohort and all cases	141265	1660674.91	3590.40	39244.68	4930	29341.79	1.37	0.7477

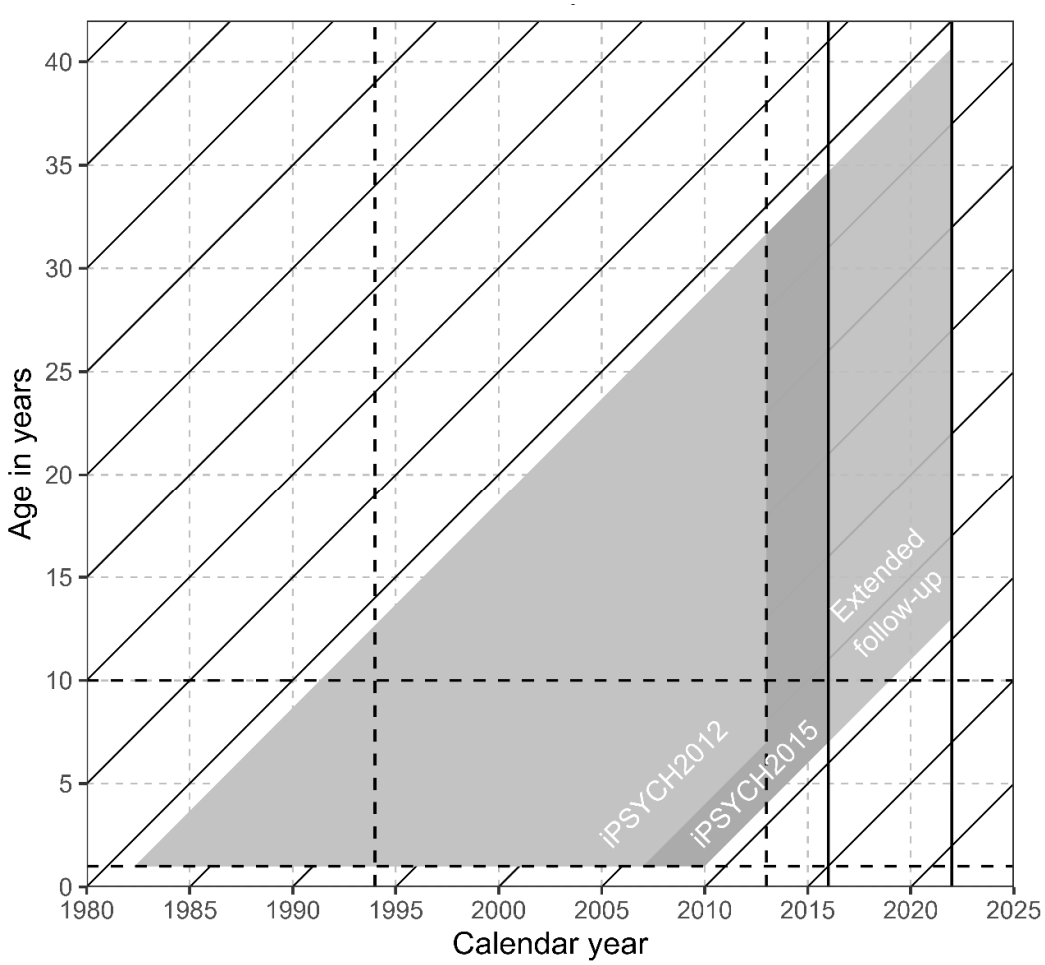
[a] Event counts are lower than in Supplementary Table 1, as they were restricted to the time period at risk, i.e. from age 1 until the disorder of interest, first emigration from Denmark, death or last follow-up.

Supplementary Table 3 Absolute risks at ages 18, 25, 30 (and 40) across samples for follow-up until 2015 and 2021.

		Follow-up until 2015 Risk (%) (95% CI)			Follow-up until 2021 Risk (%) (95% CI)			
Disorder	**Sample**	**18y**	**25y**	**30y**	**18y**	**25y**	**30y**	**40y**
Affective	Full cohort	1.09 (1.07-1.11)	3.81 (3.77-3.86)	5.63 (5.57-5.69)	1.26 (1.24-1.27)	4.12 (4.08-4.15)	5.84 (5.79-5.88)	8.01 (7.93-8.09)
	Subcohort	1.03 (0.92-1.13)	3.73 (3.49-3.96)	5.53 (5.19-5.87)	1.23 (1.13-1.33)	4.12 (3.92-4.32)	5.84 (5.58-6.10)	8.00 (7.55-8.44)
	Subcohort and outcome	1.10 (1.07-1.12)	3.81 (3.75-3.87)	5.60 (5.51-5.69)	1.30 (1.23-1.37)	4.19 (4.06-4.33)	5.90 (5.72-6.08)	8.04 (7.65-8.43)
	Subcohort and all cases	1.09 (1.07-1.12)	3.81 (3.75-3.87)	5.60 (5.51-5.69)	1.29 (1.22-1.36)	4.18 (4.05-4.31)	5.89 (5.71-6.07)	7.90 (7.54-8.26)
Epilepsy	Full cohort	1.45 (1.43-1.47)	1.87 (1.84-1.89)	2.11 (2.08-2.14)	1.41 (1.39-1.43)	1.79 (1.76-1.81)	1.99 (1.96-2.01)	2.25 (2.22-2.29)
	Subcohort	1.55 (1.43-1.67)	1.96 (1.81-2.10)	2.19 (2.02-2.36)	1.50 (1.39-1.60)	1.86 (1.73-1.99)	2.07 (1.93-2.21)	2.26 (2.09-2.42)
	Subcohort and outcome	1.55 (1.43-1.66)	1.96 (1.82-2.09)	2.20 (2.04-2.36)	1.48 (1.38-1.59)	1.85 (1.73-1.98)	2.07 (1.94-2.21)	2.27 (2.11-2.43)
	Subcohort and all cases	1.54 (1.43-1.65)	1.96 (1.82-2.09)	2.20 (2.04-2.36)	1.49 (1.39-1.60)	1.86 (1.74-1.98)	2.08 (1.95-2.21)	2.29 (2.13-2.45)

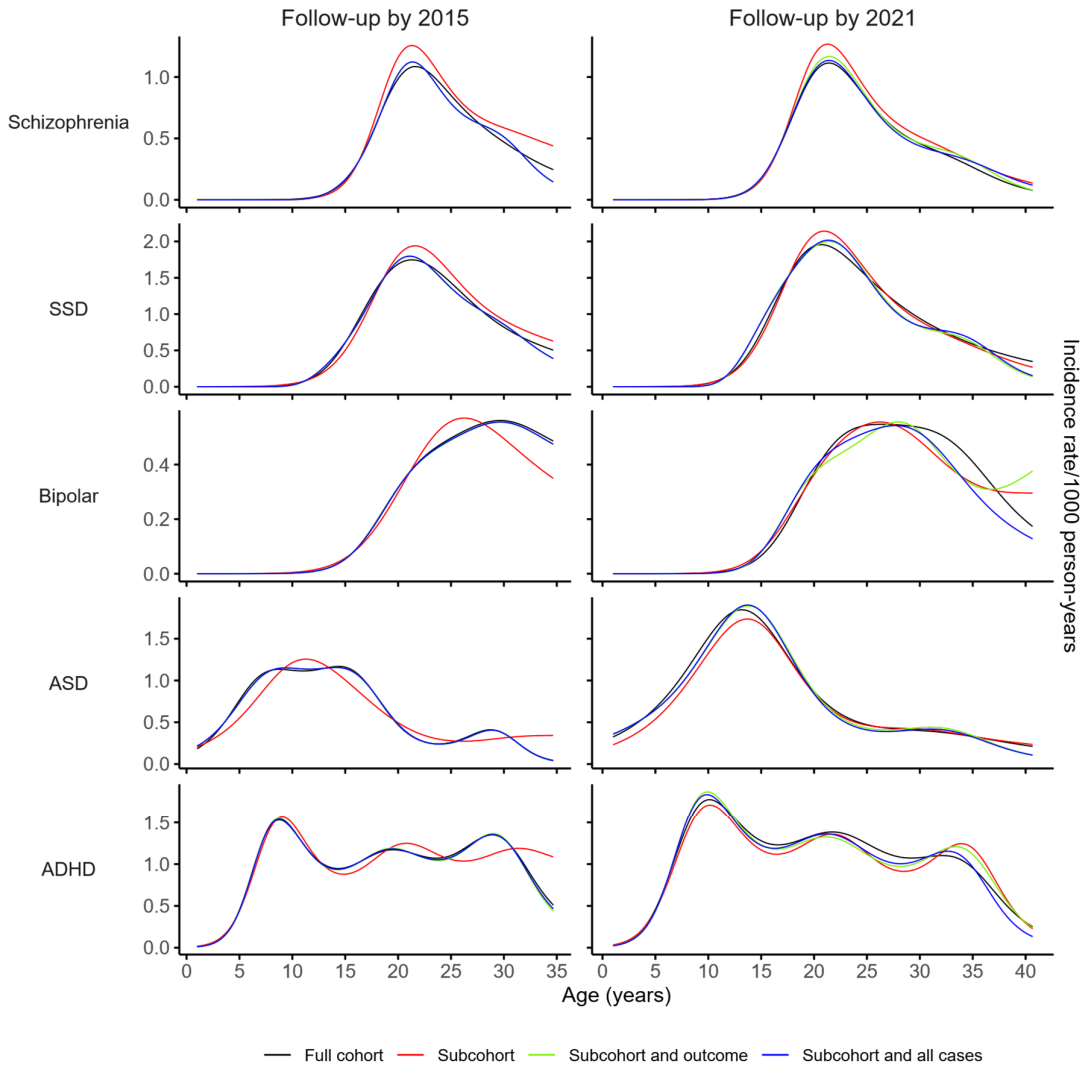
Age-specific absolute risks are shown in main Fig. 3. Extended follow-up to end of 2021 enabled estimation at age 40 years.

Supplementary Fig. 1 Lexis diagram of the iPSYCH2012- and iPSYCH2015 birth cohorts and follow-up time for identification of cases until end of 2015 and end of 2021



Ages 1 and 10 years are indicated as lower cut points of identification of diagnoses in the iPSYCH study. In the present study, all individuals were followed from age 1 (baseline).

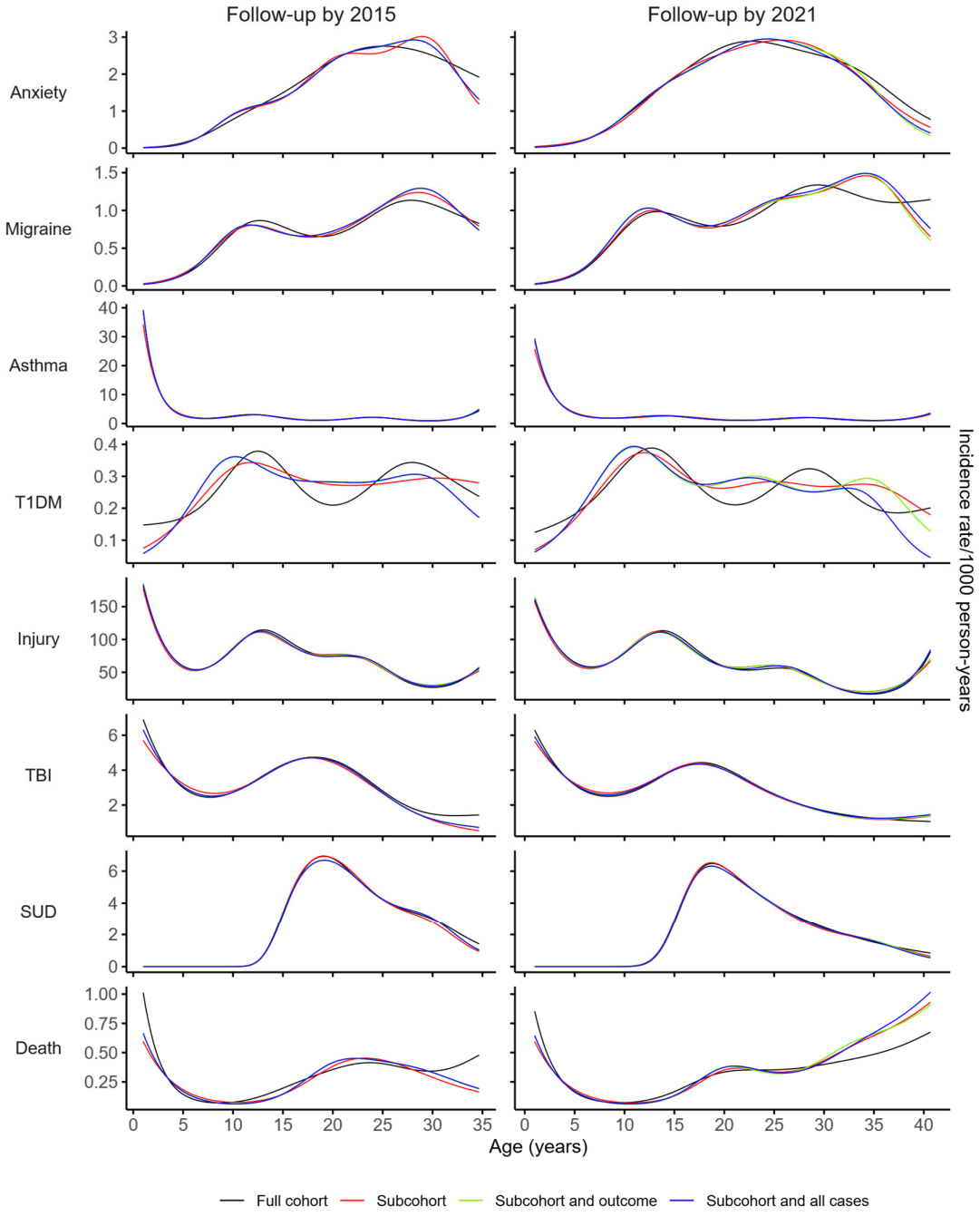
Suppementary Fig. 2 Incidence rates per 1000 person-years by age (years) and follow-up period for primary outcomes in the full cohort, iPSYCH subcohort and weighted case-cohort samples nested in the iPSYCH sample



Incidence rates were fitted from a Poisson generalised additive model with the maximum numbers of parameters (k) used for the modelling set to 7. Follow-up to 2015 (left panel) and 2021 (right panel).

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, ASD: Autism spectrum disorder, Bipolar: Bipolar disorder, SSD: Schizophrenia spectrum disorder.

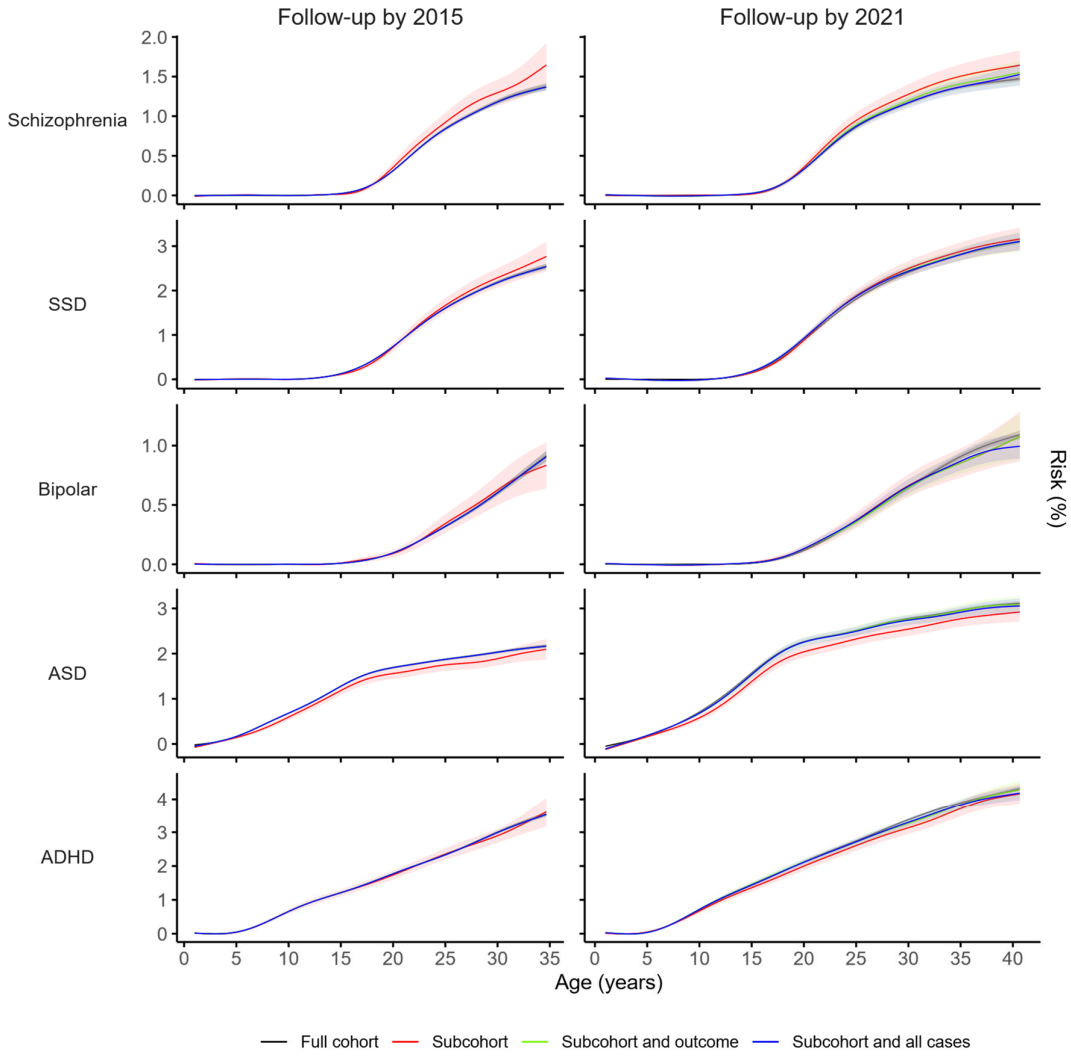
Supplementary Fig. 3 Incidence rates per 1000 person-years by age (years) and follow-up period for secondary outcomes in the full cohort, iPSYCH subcohort and weighted case-cohort samples nested in the iPSYCH sample



Incidence rates were fitted from a Poisson generalised additive model with the maximum numbers of parameters (k) used for the modelling set to 7. Follow-up to 2015 (left panel) and 2021 (right panel).

Abbreviations: Anxiety: Anxiety disorders, SUD: Substance use disorder, T1DM: Type 1 diabetes mellitus, TBI: Traumatic brain injury

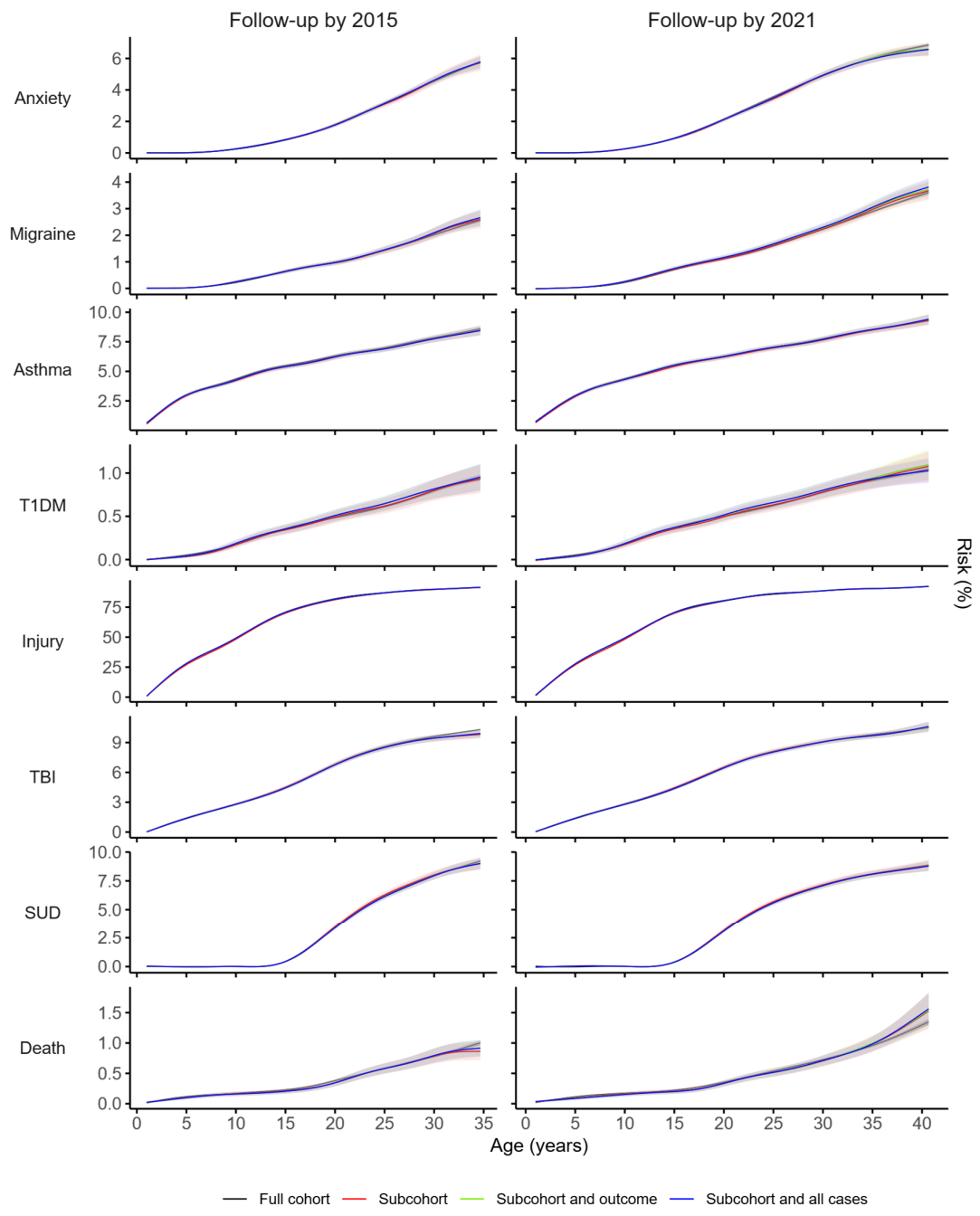
Supplementary Fig. 4 Absolute risk (%) as a function of age (years) and by follow-up period for primary outcomes in different scenarios



Curves are accompanied by 95% confidence bands, based on robust variance estimation for the case-cohort samples. Curves were smoothed using GAM-models with the maximum numbers of parameters set to 10. Follow-up to 2015 (left panel) and 2021 (right panel).

Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, ASD: Autism spectrum disorder, Bipolar: Bipolar disorder, SSD: Schizophrenia spectrum disorder.

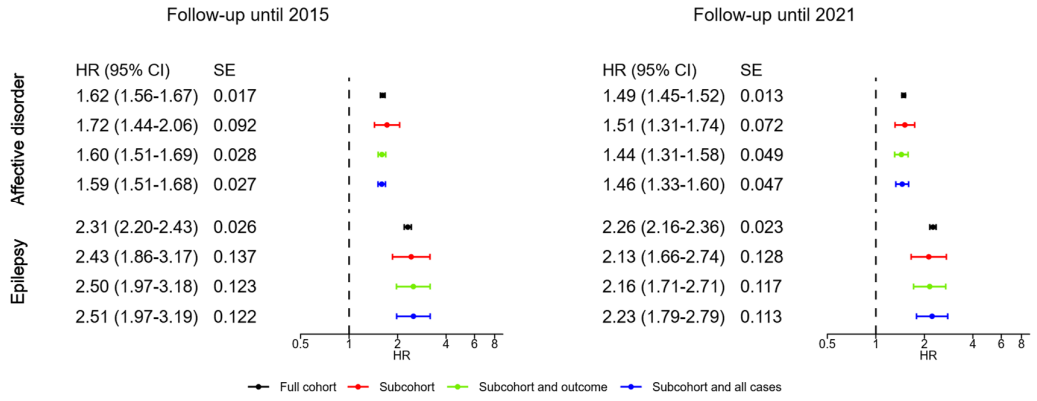
Supplementary Fig. 5 Absolute risk as a function of age (years) and by follow-up period for secondary outcomes in different scenarios



Curves are accompanied by 95% confidence bands, based on robust variance estimation for the case-cohort samples. Curves were smoothed using GAM-models with the maximum numbers of parameters set to 10. Follow-up to 2015 (left panel) and 2021 (right panel).

Abbreviations: Anxiety: Anxiety disorders, SUD: Substance use disorder, T1DM: Type 1 diabetes mellitus, TBI: Traumatic brain injury

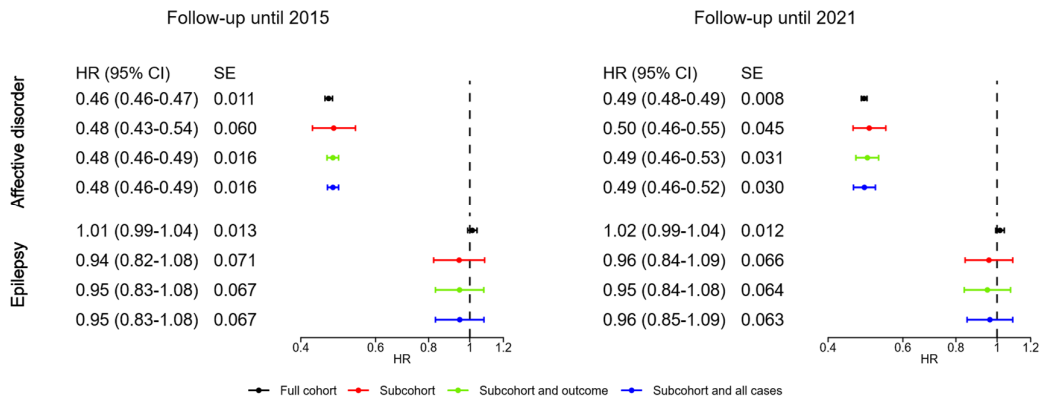
Supplementary Fig. 6 Incidence rate ratios of affective disorder and epilepsy according to a history of traumatic brain injury in the full cohort and different samples nested in the iPSYCH sample



Hazard ratios with 95% CIs were estimated from a crude Cox regression model with traumatic brain injury (secondary outcome) as a time-dependent exposure. Robust standard errors were used in the weighted models. Follow-up to 2015 (left panel) and 2021 (right panel).

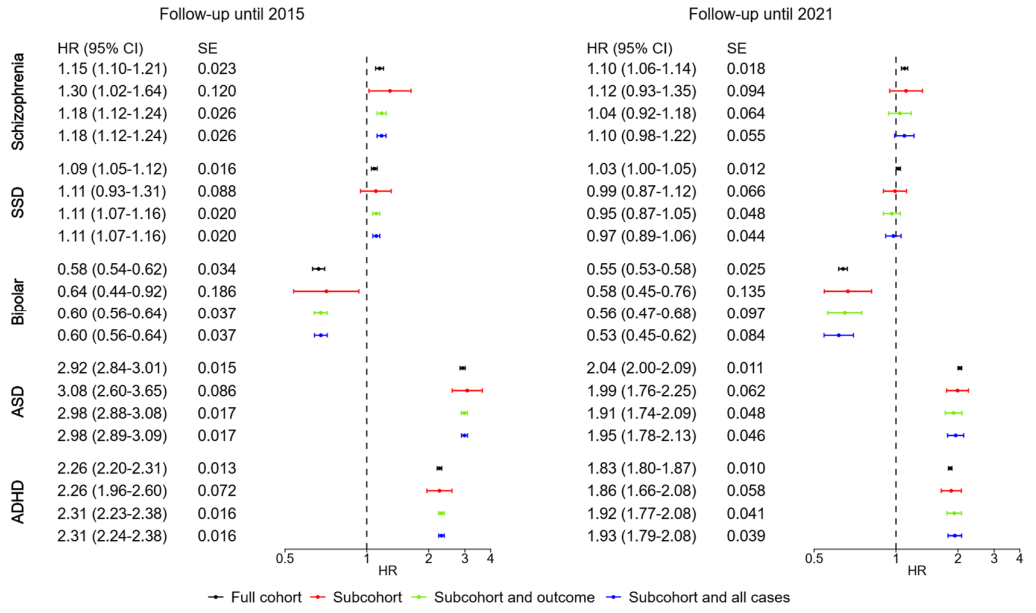
Abbreviations: CI: confidence interval, HR: Hazard ratio, se: standard error

Supplementary Fig. 7 Incidence rate ratios and 95% CIs of affective disorder and epilepsy according to sex (males vs. females) in the full cohort and different samples nested in the iPSYCH sample



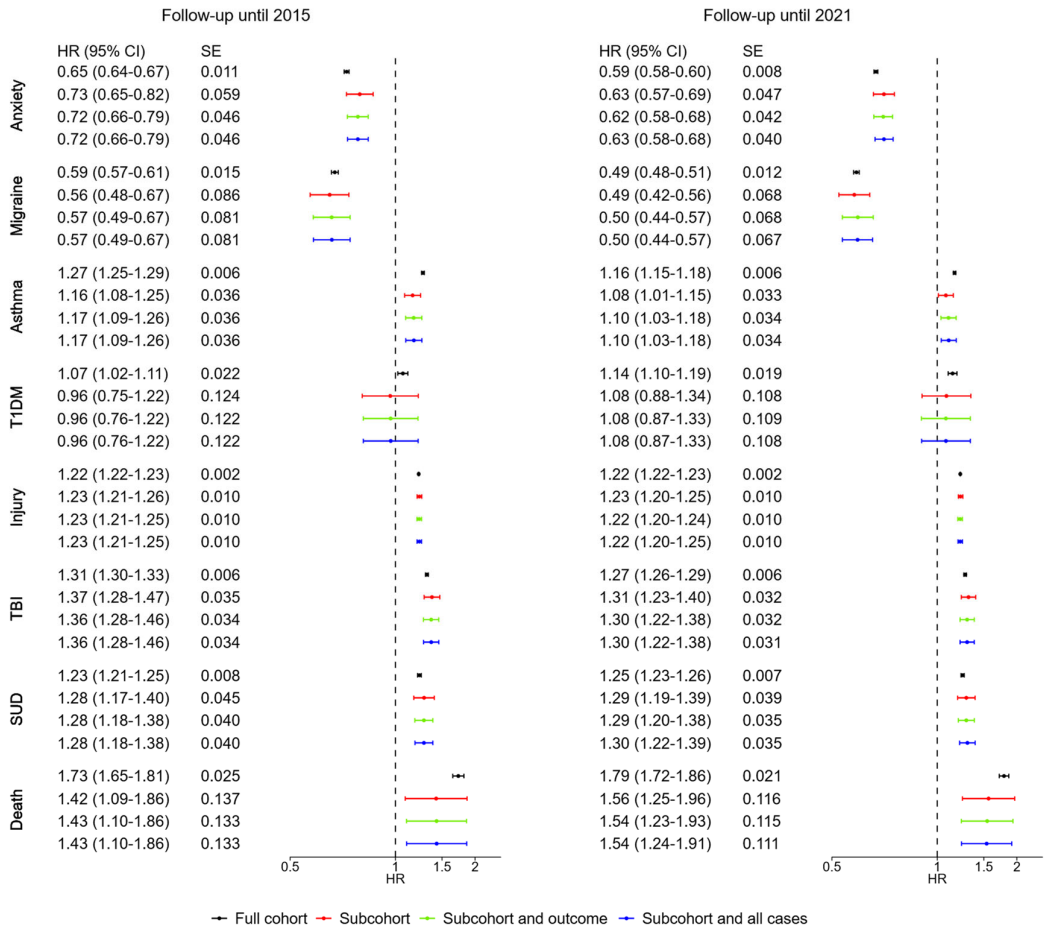
Hazard ratios with 95% CIs were estimated from a crude Cox regression model with sex as time-fixed exposure (female as reference). Robust standard errors were used in the weighted models. Follow-up to 2015 (left panel) and 2021 (right panel).
Abbreviations: CI: confidence interval, HR: Hazard ratio, SE: standard error.

Supplementary Fig. 8 Incidence rate ratios of primary outcomes according to sex (males vs. females) in the full cohort and different samples nested in the iPSYCH sample



Hazard ratios with 95% CIs were estimated from a crude Cox regression model with sex as exposure (female as reference). Robust standard errors were used in the weighted models. Follow-up to 2015 (left panel) and 2021 (right panel).
Abbreviations: ADHD: Attention-deficit/hyperactivity disorder, ASD: Autism spectrum disorder, Bipolar: Bipolar disorder, CI: confidence interval, HR: Hazard ratio, SE: standard error, SSD: Schizophrenia spectrum disorder.

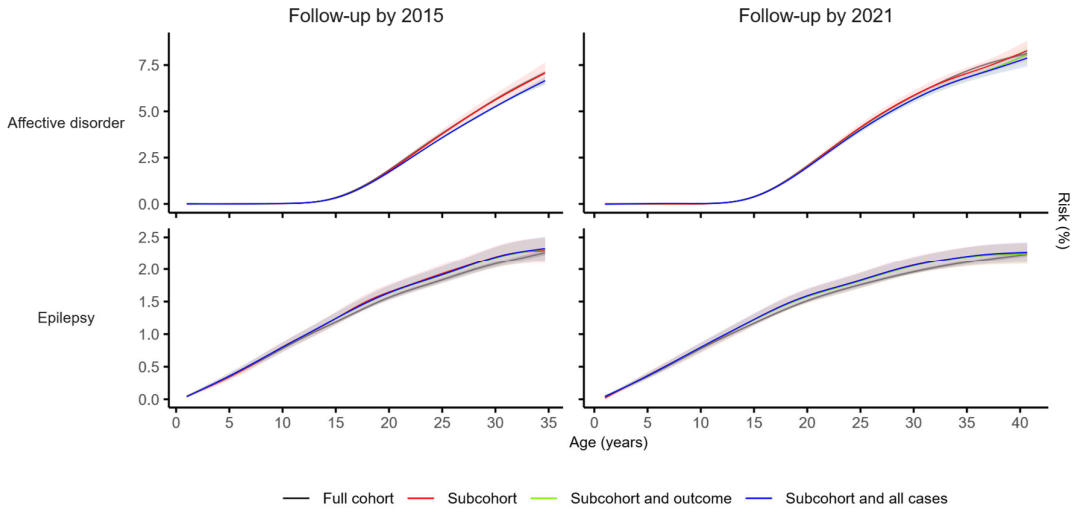
Supplementary Fig. 9 Incidence rate ratios of secondary outcomes according to sex (males vs. females) in the full cohort and different samples nested in the iPSYCH sample



Hazard ratios were estimated from a crude Cox regression model with sex as exposure (female as reference). Robust standard errors were used in the weighted models. Follow-up to 2015 (left panel) and 2021 (right panel). Follow-up to 2015 (left panel) and 2021 (right panel).

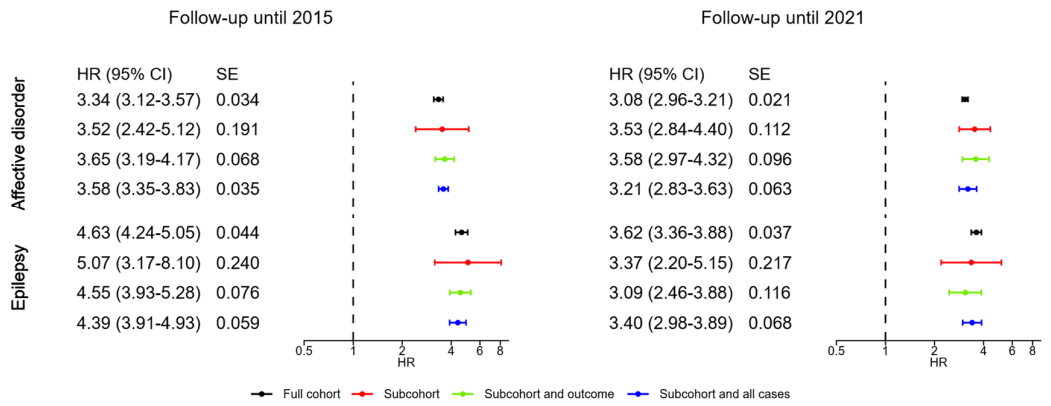
Abbreviations: Anxiety: Anxiety disorders, CI: confidence interval, HR: Hazard ratio, SE: standard error, SUD: Substance use disorder, T1DM: Type 1 diabetes mellitus, TBI: Traumatic brain injury.

Supplementary Fig. 10 Absolute risk (%) as a function of age (years) with average weights assigned to non-case subcohort members in the case-cohort samples



Curves are accompanied by 95% confidence bands, based on robust variance estimation for the case-cohort samples. Curves were smoothed using GAM-models with the maximum numbers of parameters set to 10. Follow-up to 2015 (left panel) and 2021 (right panel).

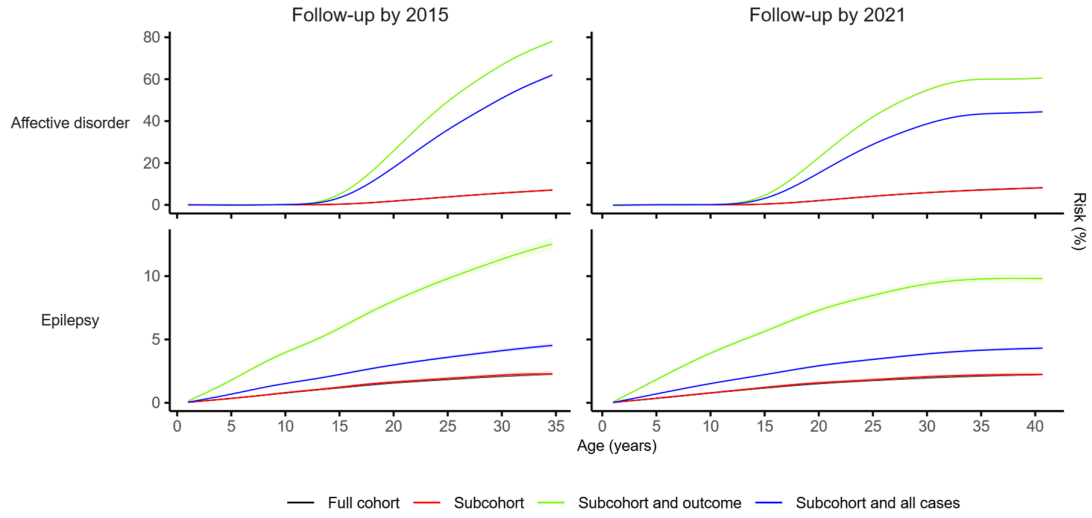
Supplementary Fig. 11 Incidence rate ratios of affective disorder and epilepsy according to a history of ASD with average weights assigned to non-case subcohort members in the case-cohort samples



Hazard ratios with 95% CIs were estimated from a crude Cox regression model with ASD (primary outcome) as a time-dependent exposure. Robust standard errors were used in the weighted models. Follow-up to 2015 (left panel) and 2021 (right panel).

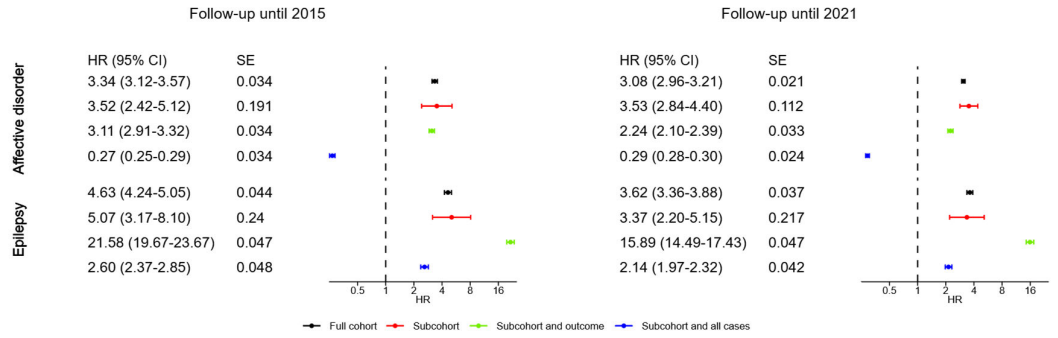
Abbreviations: ASD: Autism spectrum disorder, CI: confidence interval, HR: Hazard ratio, SE: standard error.

Supplementary Fig. 12 Unweighted absolute risk (%) as a function of age (years)



Curves are accompanied by 95% confidence bands, based on robust variance estimation for the case-cohort samples. Curves were smoothed using GAM-models with the maximum numbers of parameters set to 10. Follow-up to 2015 (left panel) and 2021 (right panel).

Supplementary Fig. 13 Unweighted incidence rate ratios of affective disorder and epilepsy according to a history of autism spectrum disorder



Hazard ratios with 95% CIs were estimated from a crude Cox regression model with ASD (primary outcome) as a time-dependent exposure. Follow-up to 2015 (left panel) and 2021 (right panel).

Abbreviations: CI: confidence interval, HR: Hazard ratio, SE: standard error

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