Table DS1.
Corrections for Regression Dilution Bias based on 4,317 participants with data from both the 1991-94 and in 2001-2003 examinations of the Copenhagen City Heart Study

Correction for Regression Dilution Bias categories

CRP levels	Participants	Mean		
		1991-94	2001-2003	
≤1.00	438	0.87	1.36	
1.01-3.00	3057	1.60	2.79	
>3.00	822	7.51	6.79	
Range of mean		6.64 (r_i)	5.43 (r_u)	
Regression dilution ratio	$\lambda = r_u/r_i$			0.82

Correction for Regression Dilution Bias quintiles

CRP quintiles	Participants	Mean		
		1991-94	2001-2003	
1st quintile	864	0.97	1.33	
2nd quintile	863	1.25	2.21	
3rd quintile	864	1.55	2.92	
4th quintile	863	2.21	3.89	
5th quintile	863	7.29	6.68	
Range of mean		6.32 (r_i)	5.35 (r_u)	
Regression dilution ratio	$\lambda = r_u/r_i$			0.85

Correction of Hazard Ratio (HR):

$$\beta \text{ coefficient} = \ln(HR)$$

$$\beta \text{ coefficient}_{corrected} = \ln(HR) / \lambda \text{ (regression dilutionratio)}$$

$$HR_{corrected} = \text{eksp} (\ln(HR) / \lambda \text{ (regression dilutionratio)})$$

Table DS2. Baseline characteristics of 78,809 individuals from the general population by endpoint

	Bipolar disorder		
	Yes	**No**	**p-value**
No. (%)	93	78,716	
Age, years, median (interquartile range)	63 (54-71)	57 (47-67)	$4*10^{-4}$
Women, No. (%)	55 (59)	43,710 (56)	0.48
Alcohol consumption, drinks/week, median (interquartile range)	4 (0-11)	8 (3-15)	0.09
Never smokers, No. (%)	24 (26)	28,928 (37)	0.03[NS]
High leisure time physical activity, more than 2-4h light/day, No. (%)	32 (34)	37,310 (47)	0.01[NS]
Less than 3 years of education*, No. (%)	63 (68)	46,579 (60)	0.09
Low income, No. (%)	35 (38)	14,102 (18)	$7*10^{-7}$
Body mass index, kg/m^2 median (interquartile range)	26 (23-29)	26 (23-28)	0.84
Chronicdisease, No. (%)	62 (67)	28,006 (36)	$4*10^{-10}$

Baseline characteristics for participants in the Copenhagen General Population Study and the Copenhagen City Heart Study combined. *Education after primary and secondary lower school. [NS] = non significant when corrected for 9 multiple comparisons (required p-value for significance 0.05/9 = 0.006)

Table DS3. Baseline characteristics of 76,479 individuals from the general population by genotype combination

	CRP genotype combinations									p-trend
	1	2	3	4	5	6	7	8	9	
No. (%)	8745	15 673	6945	16 143	14 457	2465	2273	7508	2270	
Age, years, median (interquartile range)	57 (46-67)	57 (47-67)	57 (47-67)	57 (47-67)	57 (47-67)	57 (46-67)	57 (47-67)	57 (47-67)	57 (46-67)	0.81
Women, No. (%)	4901 (56)	8692 (55)	3858 (56)	8944 (55)	7960 (55)	1355 (55)	1253 (55)	4204 (56)	1248 (55)	0.60
Alcohol consumption, g/week, median (interquartile range)	8 (3-15)	8 (3-15)	8 (3-19)	8 (3-15)	8 (3-15)	7 (3-15)	8 (3-15)	8 (3-15)	8 (3-15)	0.29
Never smoker, No. (%)	3195 (37)	5756 (37)	2561 (37)	5926 (37)	5350 (37)	902 (37)	815 (36)	2791 (37)	818 (36)	0.81
High leisure time physical activity, more than 2-4h light/day, No. (%)	3995 (45)	7496 (48)	3380 (49)	7551 (47)	6898 (48)	1202 (49)	1116 (49)	3584 (48)	1111 (49)	0.02[NS]
Less than 13 years of education, No. (%)*	5225 (60)	9264 (60)	4016 (58)	9577 (60)	8552 (60)	1438 (59)	1368 (61)	4522 (61)	1381 (61)	0.10
Low income, No. (%)	1543 (18)	2789 (18)	1172 (17)	2918 (18)	2516 (17)	462 (19)	416 (18)	1358 (18)	391 (17)	0.51
Body mass index, median (interquartile range)	26 (26-29)	26 (23-28)	26 (23-28)	25 (23-28)	25 (23-28)	25 (23-28)	26 (23-28)	25 (23-28)	25 (23-28)	0.02[NS]
Chronicdisease, No. (%)	3171 (36)	5584 (36)	2415 (35)	5708 (35)	5115 (35)	881 (36)	778 (34)	2698 (36)	765 (34)	0.22

Baseline characteristics for participants in the Copenhagen General Population Study and the Copenhagen City Heart Study combined. Individuals with rare genotype combinations were excluded. *Education after primary and secondary lower school. [NS] = non significant when corrected for 9 multiple comparisons (required p-value for significance 0.05/9 = 0.006)

Table DS4. Diagnoses of bipolar disorder of the 93 individuals with a hospitalization/death with bipolar disorder

Diagnosis	ICD8	ICD10	No.
Manic-depressive psychosis, manic type	296.19		13
Manic-depressive psychosis, circular type	296.39		4
Mania withoutpsychotic symptoms		DF30.1	1
Mania with psychotic symptoms		DF30.2	2
Othermanic episodes		DF30.8	3
Manic episode, unspecified		DF30.9	6
Bipolar affective disorder, current episode hypomanic		DF31.0	2
Bipolar affective disorder, current episode manic without psychotic symptoms		DF31.1	3
Bipolar affective disorder, current episode manic with psychotic symptoms		DF31.2	5
Bipolar affective disorder, current episode mild or moderate depression		DF31.3	8
Bipolar affective disorder, current episode severe depression without psychotic symptoms		DF31.4	3
Bipolar affective disorder, currently in remission		DF31.7	1
Other bipolar affectivedisorders		DF31.8	1
Bipolar affectivedisorder, unspecified		DF31.9	41
Total			93

Diagnoses for participants with a hospitalization/death with bipolar disorder in the Copenhagen General Population Study and the Copenhagen City Heart Study combined.

Table DS5.
The effect of the CRP SNPs on expression levels, i.e. whether they are expression quantitative trait loci (eQTLs) from the SCAN database(www.scandb.org).

rs1205

Gene name (dataset)	p-value	Protein	Association with disease
ADAM15 (PDS)	0.0006306	ADAM15 = ADisintegrin And Metalloproteinase 15 An enzyme encoded by the ADAM15gene and member of the ADAM family of transmembrane glucoproteins with effects on cell adhesion, migration and signalling.[1]	Rheumatoid arthritis[2] and cancer[3]
LMNA (PDS)	0.0072280	LMNA = Lamin A Lamins arestructural protein components of the nuclear lamina, which underlie the inner nuclear membrane that determines nuclear shape and size.[4]	Laminopathiesincluding Emery Dreifuss muscular dystrophy, limb girdle muscular dystrophy, congenital muscular dystrophy-L, dilated cardiomyopathy, Hutchinson-Gilford progeria syndrome, restrictive dermopathy (RD) ect.[4]
SEMA4A (PDS)	0.0090680	SEMA4A = Semaphorin 4A Aglucoprotein and member of the semaphorin family of secreted and membrane-bound glycoproteins that regulate thefunctional activity of axons in the nervous system.[5]	Possibly involved in astma, cancer, autoimmune diseases, cardiovascular disease, renal diseases, and infectious diseases.[5]
SDHC (PDS)	0.0030830	SDHC = Succinate dehydrogenase C The succinate dehydrogenase protein consists of four subunits (A, B, C, D)and is a key enzyme of the citric acid cycle. The SDHC gene is alsoa tumor suppressor gene.[6]	Mutations in the SDH genes have been associated with paragangliomas,renal carcinoma, and gastrointestinal stromal tumors.[6]
SHC1 (PDS)	0.0065470	SHC = Src homology and collagen homolog The SHC1 (SHCA) gene codes for the three proteins p52shc, p46shc, and p66shc which regulate functions as diverse as growth(p52shc/p46shc), apoptosis and life-span (p66shc)[7]	Cancers including prostate cancer and breast cancer[7]

rs1130864

Gene name (dataset)	p-value	Protein	Association with disease
LMNA (PDS)	0.0073050	LMNA = Lamin A Lamins are structural protein components of the nuclear lamina, which underlie the inner nuclear membrane that determines nuclear shape and size.[4]	*Laminopathies* including Emery Dreifuss muscular dystrophy, limb girdle muscular dystrophy, congenital muscular dystrophy-L, dilated cardiomyopathy, Hutchinson-Gilford progeria syndrome, restrictive dermopathy (RD) ect.[4]
FCER1A (PDS)	0.0035550	FCER1A = high-affinity immunoglobulin E receptor 1 alfa The high-affinity immunoglobulin E receptor consists of four subunits: one alfa subunit (FCER1A), two beta subunits and one gamma subunit.[8]	Asthma[9]
IGSF9 (PDS)	0.0071890	IGSF9 = immunoglobulin superfamily member 9 A large family of immunoglobulin proteins mediating signal transduction between an extracellular ligand and second-messenger cascades within the cell.[10]	?
C1orf192 (CDS)	0.007828	Myelin protein zero The most abundant myelin protein in the peripheral nervous system.[11]	Charcot-Marie-Tooth Disease[12]

rs3093077

Gene name (dataset)	p-value	Protein (OMIM)	Association with disease
RASSF7 (AFF)	0.00005	RASSF7= RAS-association domain family member 7 Member of the RAS-association domain family (RASSF) of proteins with roles in regulation of cell growth and apoptosis.[13]	Cancer[13]

Dataset in the SCAN database:
PDS= parietal dataset. CDS= cerebellum dataset. AFF= affymetrix 6.0 eQTL annotation (whole human exome)

References

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(12) Maeda MH, Mitsui J, Soong BW et al. Increased gene dosage of myelin protein zero causes Charcot-Marie-Tooth disease. *Ann Neurol* 2012;71:84-92.

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SNP	Minor allele frequency	Chromosome 1 position
rs1205: G→A	A: 0.34	159712443
rs1130864: C→T	T: 0.31	159713301
rs3093077: T→G	G: 0.05	159709846
rs3091244: C→T→A	T: 0.31	159714875
	A: 0.05	

C-allele vs. A/T
for rs3091244

T-allele vs. C/A
for rs3091244

A-allele vs. C/T
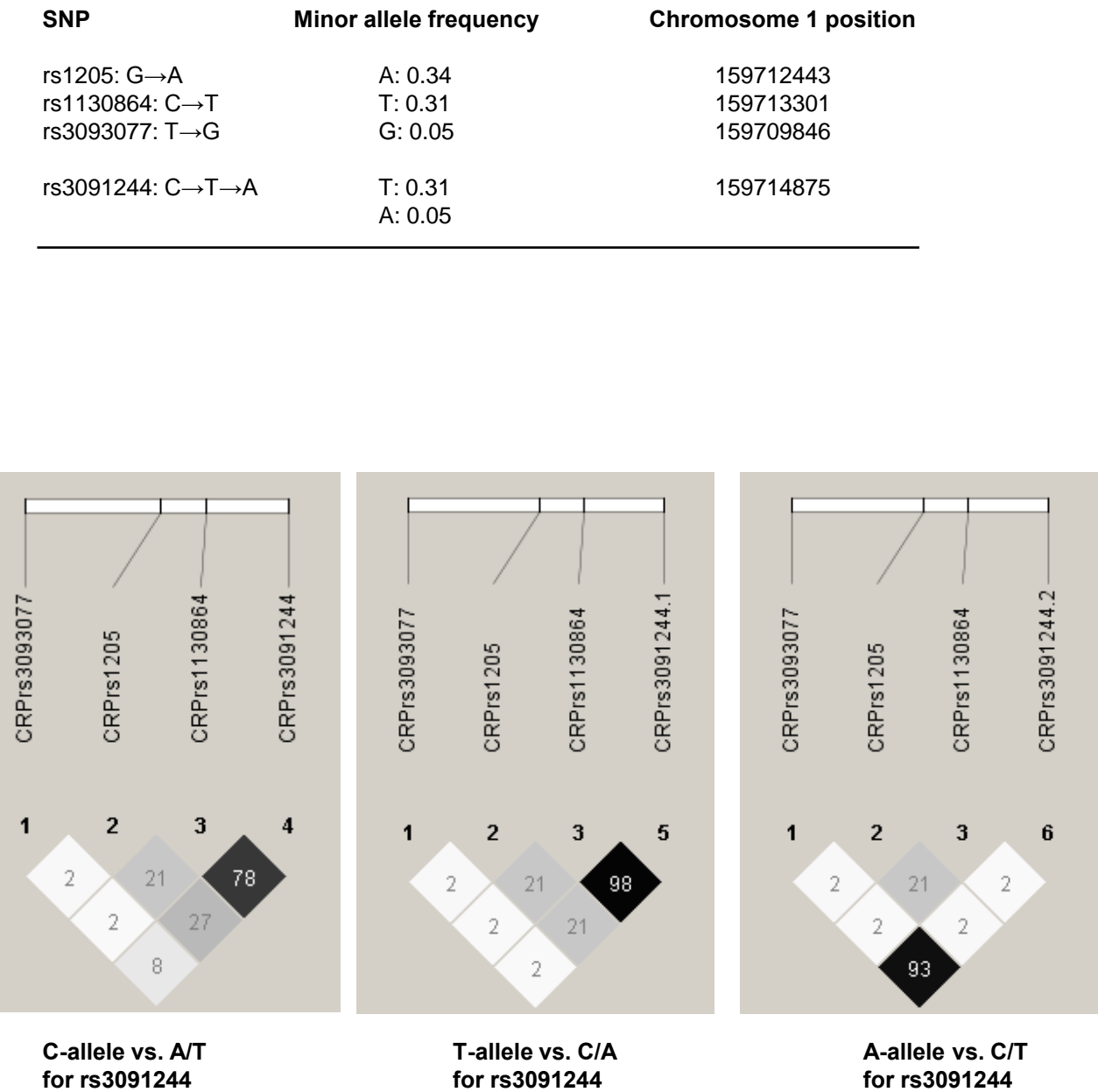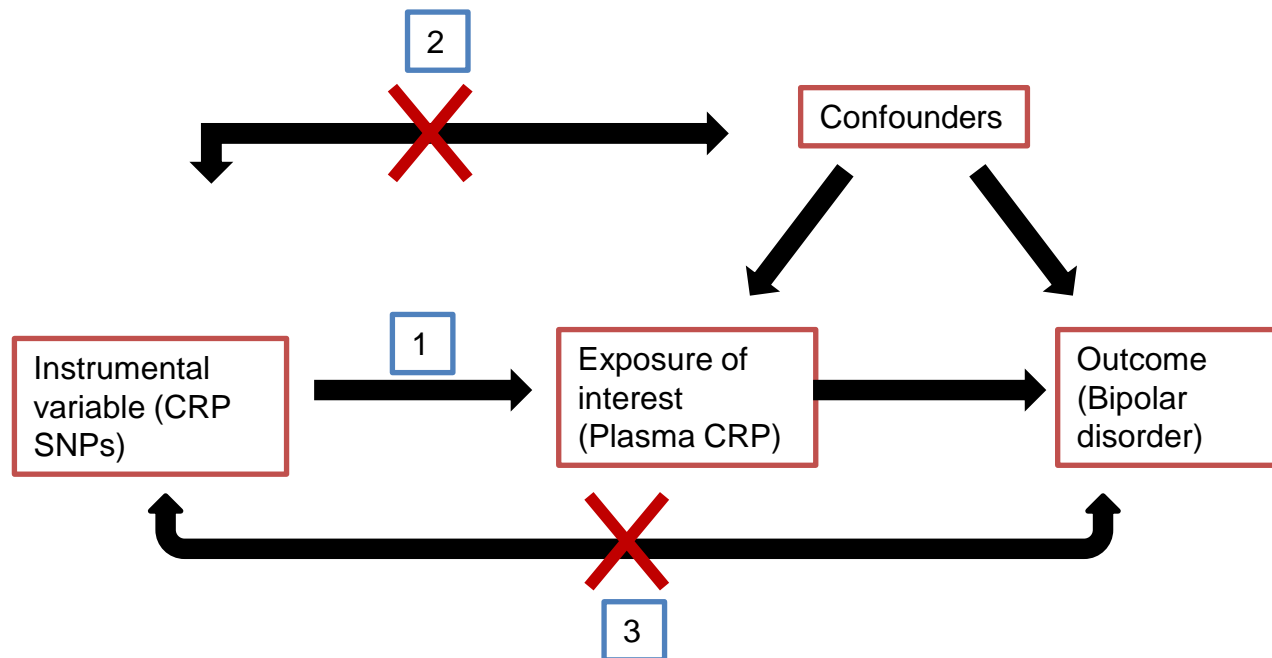for rs3091244

Fig. DS1
Linkage disequilibrium plot of rs3093077, rs1205, rs1130864, and rs3091244. Including all
participants in the Copenhagen General Population Study and the Copenhagen City Heart
Study. The numbers in the squares are R^2-values in percent. SNP = single nucleotide
polymorphism.

Fig. DS2
Schematic graph of the instrumental variable analysis and assumptions.

CRP levels (mg/L)	Median CRP (mg/L)	No.	Events	Incidence rate (events/10,000)	Unadjusted	Age and gender adjusted	Multifactorially adjusted
Cross-sectional analyses							
≤ 1.00	0.60	14,832	10	7	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.01–3.00	1.51	48,230	47	10	2.29 (1.00-5.28)	2.13 (0.90-5.08)	1.40 (0.61-3.26)
3.01–10.00	4.52	13,008	27	21	4.62 (1.95-10.9)	4.13 (1.68-10.1)	2.44 (0.97-6.16)
> 10.00	15.4	2739	9	33	7.64 (2.64-22.2)	6.72 (2.21-20.5)	3.48 (1.11-10.9)
1. quintile	0.63	15,809	13	8	1.00 (reference)	1.00 (reference)	1.00 (reference)
2. quintile	1.20	15,734	15	10	1.72 (0.69-4.26)	1.65 (0.66-4.09)	1.21 (0.50-2.91)
3. quintile	1.52	15,744	11	7	1.22 (0.46-3.24)	1.10 (0.41-2.93)	0.76 (0.29-1.97)
4. quintile	2.20	15,775	18	11	1.96 (0.83-4.63)	1.69 (0.71-4.02)	1.13 (0.48-2.67)
5. quintile	5.04	15,747	36	23	3.95 (1.86-8.38)	3.33 (1.55-7.13)	1.99 (0.90-4.40)

Odds ratio (95% confidence interval)

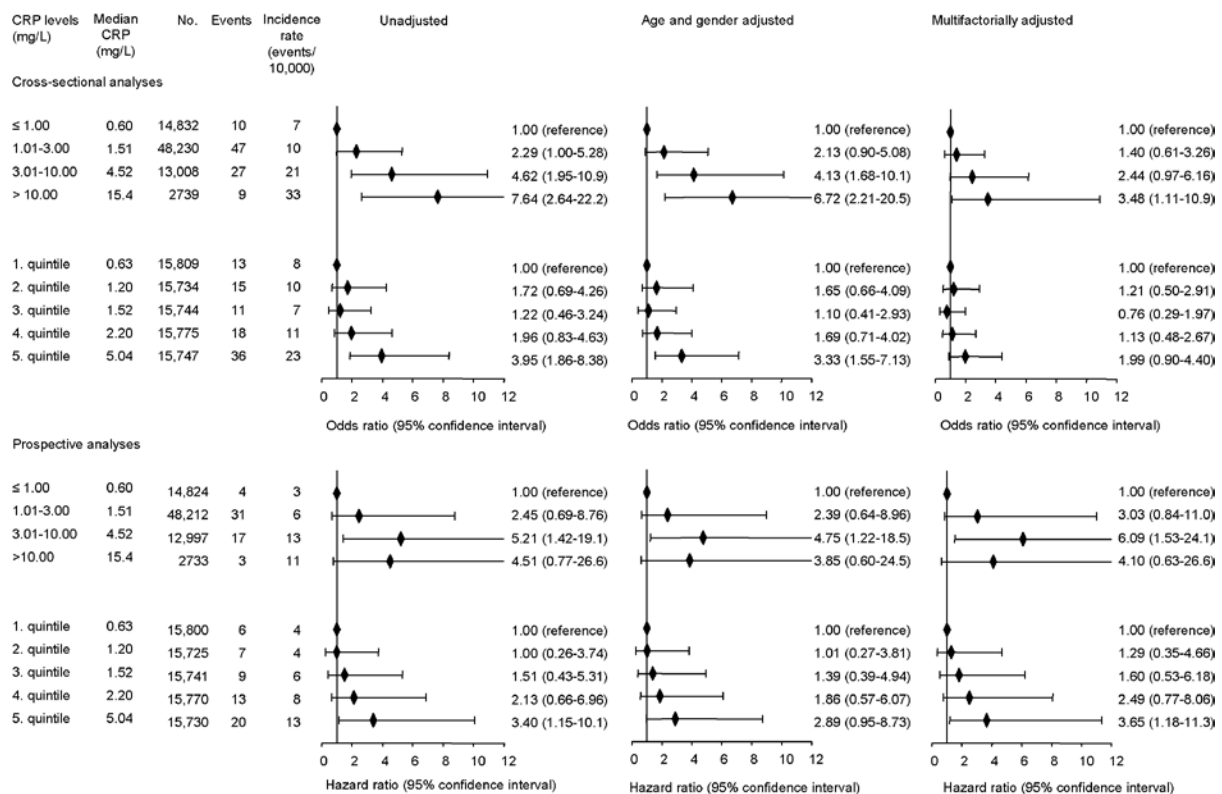| CRP levels (mg/L)	Median CRP (mg/L)	No.	Events	Incidence rate (events/10,000)	Unadjusted	Age and gender adjusted	Multifactorially adjusted
Prospective analyses							
≤ 1.00	0.60	14,824	4	3	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.01–3.00	1.51	48,212	31	6	2.45 (0.69-8.76)	2.39 (0.64-8.96)	3.03 (0.84-11.0)
3.01–10.00	4.52	12,997	17	13	5.21 (1.42-19.1)	4.75 (1.22-18.5)	6.09 (1.53-24.1)
>10.00	15.4	2733	3	11	4.51 (0.77-26.6)	3.85 (0.60-24.5)	4.10 (0.63-26.6)
1. quintile	0.63	15,800	6	4	1.00 (reference)	1.00 (reference)	1.00 (reference)
2. quintile	1.20	15,725	7	4	1.00 (0.26-3.74)	1.01 (0.27-3.81)	1.29 (0.35-4.66)
3. quintile	1.52	15,741	9	6	1.51 (0.43-5.31)	1.39 (0.39-4.94)	1.60 (0.53-6.18)
4. quintile	2.20	15,770	13	8	2.13 (0.66-6.96)	1.86 (0.57-6.07)	2.49 (0.77-8.06)
5. quintile	5.04	15,730	20	13	3.40 (1.15-10.1)	2.89 (0.95-8.73)	3.65 (1.18-11.3)

Hazard ratio (95% confidence interval)

Fig. DS3
Cross-sectional and prospective analyses of the associations between clinical categories of CRP or CRP quintiles and bipolar disorder in the general population.

Based on 78 809 participants from the Copenhagen General Population Study and the Copenhagen City Heart Study combined, followed for up to 20 years (median 5.9 years; interquartile range: 4.4–7.6). Participants with previous or current bipolar disorder at baseline (*n*=38) were excluded in the prospective analysis. For the unadjusted prospective model the underlying time scale was follow-up time, otherwise age was the underlying time scale. Multifactorially adjusted was for age, gender, alcohol consumption, smoking status, physical activity, level of education, level of income, body mass index and chronic disease. CRP=C-reactive protein.
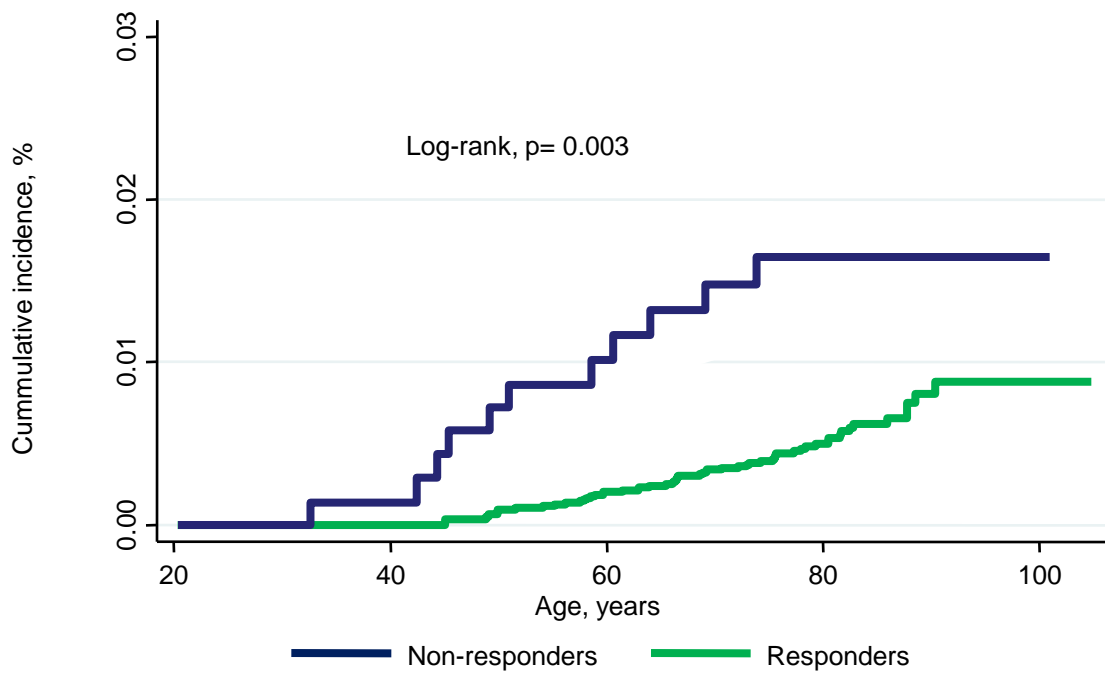
Fig. DS4
The cumulative incidence of bipolar disorder among responders and non-responders as a function of age. Based on 24,260 individuals from all examinations of the Copenhagen City Heart Study starting in 1976; Responders: N = 18,974. Non-responders: N = 5,286.