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Impact of non-participation bias due to psychiatric illness on mortality and cardiovascular event estimates: a Danish longitudinal population study

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ABSTRACT

Objectives The impact of non-participation due to psychiatric illness on study outcomes in general population studies is insufficiently investigated. Here, we investigate the mental health bias in a population study and the potential impact on estimates of cardiovascular morbidity and overall survival.

Design Data were retrieved from nationwide registries.

Setting The Danish General Suburban Population Study (GESUS), a cross-sectional community study conducted in Naestved Municipality, Denmark, from 2010 to 2013.

Participants 49 707 subjects invited to participate in GESUS.

Main outcome measures Factors related to non-participation were examined using multivariable logistic regression and time-to-event data using Cox proportional hazards models.

Results Of 21 203 (43%) participants, 823 (3.9%) had a psychiatric diagnosis. Of 28 504 non-participants, 2453 (8.6%) had a psychiatric diagnosis (OR for non-participation 1.84 (95% CI 1.69 to 2.00)). The most under-represented psychiatric disorders in participants were organic mental disorders (5.76 (3.90 to 8.48)), substance abuse (3.12 (2.14 to 4.54)) and schizophrenia (3.12 (2.33 to 4.18)). Overall, more non-participants used psychotropic drugs than participants (1.26 (1.21 to 1.31)), and psychiatric non-participants had higher psychiatric hospital service utilisation than psychiatric participants. Compared with non-psychiatric participants in a 5-year follow-up, psychiatric non-participants had higher rates of cardiovascular events (HR 2.30 (2.07 to 2.56)) and all-cause mortality (3.37 (3.01 to 3.78)) than non-psychiatric non-participants (1.65 (1.48 to 1.83) and 2.26 (2.02 to 2.54), respectively) and psychiatric participants (1.39 (1.21 to 1.59) and 1.23 (1.05 to 1.44), respectively), $p_{interaction}<0.0001$ for both outcomes.

Conclusions This study demonstrates a considerable non-participation bias due to psychiatric illness in a general population health study, potentially leading to distorted estimates of somatic morbidity and mortality. Strategies for better-representing individuals with psychiatric illnesses in population health studies are needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psychiatric disorders are associated with increased somatic morbidity and premature death. Previous investigations have shown that people with psychiatric illnesses are under-represented in population health studies.

WHAT THIS STUDY ADDS

⇒ We demonstrate considerable non-participation bias due to psychiatric illness in a population study potentially leading to distorted estimates of both somatic morbidity and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In general health studies, we need initiatives to ensure a better representation of individuals with psychiatric illnesses to provide accurate estimates of disease burden for strategies in public health efforts, particularly those aimed at individuals with psychiatric conditions.

INTRODUCTION

Psychiatric disorders are associated with increased somatic morbidity and premature death, primarily due to preventable and treatable somatic diseases such as ischaemic heart disease, stroke, cancer, chronic lung diseases and infections.[1–5] A reduced life expectancy of up to 10–20 years in severe mental disorders, for example, schizophrenia and other psychotic disorders, bipolar disorder and severe depression has been demonstrated.[6–12] Thus, to accurately estimate the population's health profile and disease burden, psychiatric patients must be represented in general population studies, as they may disproportionately contribute to disease burden and mortality in the population. Population studies usually require invited subjects to consent to participate, entailing a risk of selection bias and consequently

distortion of study estimates. Well-known determinants of non-participation include sociodemographic factors such as young and old age, male sex, not being married, low socioeconomic status (SES) and foreign country of origin.[13–17]

Results from previous studies suggest an association between non-participation and psychiatric illness.[15 18–23] In both a Finnish[18] and Norwegian[19] general health population survey and a Swedish population study on mental health,[20] registry-based hospital-treated psychiatric illness was associated with non-participation. A population-based study in Norway[15] estimated the prevalence of psychiatric illness in non-participants versus participants based on data from questionnaires and a random sample of general practice patient records and similarly found that psychiatric illness prevalence was increased among non-participants. Another Norwegian population study[21] found that recipients of disability pension due to substance abuse, psychotic disorders or personality disorders were highly over-represented among non-participants. In studies of the Danish national breast cancer screening programme (Danish women aged 50–69 years)[22] and the Danish national colorectal cancer screening programme (all Danish residents aged 50–74 years),[23] people with mental disorder, defined as previous psychiatric diagnoses or use of psychoactive prescription medicine, were less likely to participate in the screening programmes compared with people without a history of mental disorders.

Based on the above evidence, we hypothesised that psychiatric diagnoses and psychotropic drug use would be more prevalent in the Danish General Suburban Population Study (GESUS) non-participants than participants, that psychiatric illness in the non-participant group would be of overall higher severity, and that the highest rates of cardiovascular events and all-cause mortality would be observed in the group of non-participating psychiatric patients.

No previous studies have to our knowledge investigated the potential impact of non-participation of psychiatric individuals on population study estimates of somatic morbidity and overall survival.

This present investigation is based on GESUS, a large general population health study cohort, in which we exploited that comprehensive registry-based health data were available for participants and non-participants alike. This enabled us to (1) characterise the distribution of all psychiatric diagnostic groups (cf. WHO *International Classification of Diseases* 10th revision (ICD-10)) and the use of psychiatric hospital services in GESUS non-participants compared with GESUS participants, (2) describe the use of psychotropic drugs in non-participants versus participants, (3) investigate the association between psychiatric morbidity and cardiovascular events and all-cause mortality in a 5-year follow-up and (4) test if participation status interacted with this association.

METHODS

The Danish General Suburban Population Study (GESUS)

GESUS, a cross-sectional community study, was conducted in Naestved Municipality in Denmark with inclusion from January 2010 to October 2013. In total, 49 807 individuals fulfilled the inclusion criteria: (1) Danish citizenship, (2) a Danish Civil Registration number and (3) a registered address in Naestved Municipality (postal codes: DK-4160, DK-4171, DK-4250, DK-4262, DK-4684, DK-4700, DK-4733, DK-4736). All individuals over the age of 30 as well as a random sample of 25% of the population aged 20–30 years were invited. Invitations were sent by mail with continuous enrolment and in case of no response, a second invitation was sent. The subjects were asked to fill out a self-administered questionnaire concerning health-related information prior to attending a clinical examination and blood and urine sampling at Naestved University Hospital, Denmark. Further details on GESUS were described elsewhere.[24]

Study design

Data on GESUS participants and non-participants were retrieved from Danish nationwide administrative and health registries. We investigated previous psychiatric diagnoses, use of psychiatric hospital services and redeemed psychotropic drug prescriptions, as well as sociodemographic characteristics of non-participants versus participants at study invitation. In a longitudinal design with a 5-year follow-up, we investigated major adverse cardiovascular events (MACEs) and all-cause mortality in non-participants versus participants with and without psychiatric morbidity.

Registries

Sociodemographic data used for assessing eligibility including Danish citizenship, birthday and residence, and data on sex, country of origin and marital status of all invited subjects were collected from the Danish Civil Register.[25] Data on psychiatric diagnoses and use of psychiatric hospital services were retrieved from the Danish Psychiatric Central Research Register in which data on all psychiatric hospital admissions in Denmark since 1970 and visits in psychiatric outpatient and acute clinics since 1995 are registered with associated psychiatric diagnoses.[26] Only psychiatric diagnoses defined in ICD-10, implemented in Denmark in January 1994, and only the principal diagnosis for each hospital contact were included. A single main psychiatric diagnosis was defined for each subject as the numeric lowest registered ICD-10 diagnosis in line with the hierarchical order in ICD-10 *Chapter V Mental and behavioural disorders* (F00–F99). F10–F19 diagnoses (substance abuse disorders) were only defined as the main psychiatric diagnosis if no other psychiatric diagnoses were registered.

Data on psychotropic drug use were collected from the Danish National Prescription Registry in which detailed information on every redeemed prescription from any Danish community pharmacy is registered since 1995.[27]

Anatomical Therapeutic Chemical codes N05 (psycholeptics), N06 (psychoanaleptics) and N07D (drugs used in addictive disorders) were included. N06C (psycholeptics and psychoanaleptics in combination) drugs are not used in Denmark and were not included. Antiepileptics used for psychiatric indications, valproic acid (N03AG01) and lamotrigine (N03AX09) were only included in the absence of any epilepsy diagnosis at study invitation, retrieved from the Danish National Patient Registry.[28]

Data on hospital contacts due to MACEs were retrieved from the Danish National Patient Registry.[28] A traditional 3-point MACE definition including acute myocardial infarction (ICD-10 I21), stroke (ICD-10 I60–I61, I63–I64, H34.1, G45) and cardiovascular death (ICD-10 I00–I99) was used.[29] Data on deaths including manner and cause (ICD-10 diagnosis) were collected from the Danish Register of Causes of Death.[30]

Income and highest attained education, at the year of study invitation, were used as indicators of SES. Data were retrieved from the Danish Income Statistics Register[31] and the Danish Population's Education Register,[32] respectively.

Definitions

Psychiatric morbidity was defined as present if at least one of the two following criteria were fulfilled: (1) subjects diagnosed with a WHO ICD-10 Chapter V *Mental and behavioural disorders* (F00–F99) diagnosis at any time prior to study invitation and (2) subjects with a total of at least three redeemed prescriptions for any psychotropic drug at any time prior to study invitation.

Statistical analyses

Logistic regression models were used to estimate ORs for non-participation with 95% CIs. Time-to-event data of all-cause mortality and MACE were right-censored. Unadjusted overall survival functions were estimated using the Kaplan-Meier method and tested for equality using a log-rank test. Cumulative incidence functions of MACE were estimated in the presence of competing risks (non-cardiovascular death) and tested for equality using Gray's test. We estimated the incidence rates (IRs) and used Cox proportional hazards regression models to estimate HRs of MACE and all-cause mortality with 95% CIs. The proportional hazards assumption was evaluated by graphical assessment of the Schoenfeld residuals and was met in each model. A likelihood ratio test was used to assess the interaction between psychiatric morbidity and GESUS participation status in models of all-cause mortality and MACE, and a two-sided p value less than 0.05 was considered statistically significant. All estimates were presented as crude, adjusted for sex and age and further adjusted for the confounding potential of sociodemographic factors on participation status, including country of origin, residence, marital status and SES indicated by highest attained education. Estimates on psychotropic drug use and psychotropic drug groups were further adjusted for co-occurrence of any psychiatric diagnosis and use of other psychotropic drugs, respectively. All statistical analyses were performed using R V.4.0.3 (R Core Team (2020), Vienna, Austria).

Patient and public involvement

Participants and the public were not involved in the planning and conduction of this research.

Data sharing statement

All data are housed at secured servers at Statistics Denmark with encrypted personal registration numbers. Aggregated data can be exported from Statistics Denmark but not individual data. Access to the study data is only allowed to foreign researchers with an affiliation to a recognised Danish research organisation.

RESULTS

A total of 49 807 Danish adults living in Naestved Municipality were defined as eligible for an invitation to participate in GESUS from 2010 to 2013. Due to the ongoing enrolment design, 100 were registered dead before receiving the invitation and hence excluded. Of the remaining 49 707 subjects, 21 203 (42.7%) consented to participate (figure 1). Table 1 lists the baseline sociodemographic characteristics of participants and non-participants. Compared with participants, non-participants were more often men (OR for non-participation 1.36 (1.31 to 1.41)), younger than 40 (OR for non-participation 2.95 (2.76 to 3.15)), originating outside the Northern countries (Denmark, Norway, Sweden, Finland, Greenland, Iceland, Faroe Islands) (OR for non-participation 1.12 (0.98 to 1.27)), residing in the rural part of Naestved Municipality (OR 1.20 (1.15 to 1.25)), not married (OR for non-participation among widowed 1.78 (1.65 to 1.92), unmarried 1.71 (1.62 to 1.81) and divorced 1.66 (1.57 to 1.75)) and had an overall lower SES indicated by highest attained education (OR for non-participation among individuals with basic education 1.81 (1.70 to 1.93)) and annual personal income (OR for non-participation among individuals with an income in the first quartile 1.77 (1.66 to 1.89)). Information on marital status was obtained after inclusion and was missing in 1818 subjects who died before the data extraction. A total of 997 subjects finished their education before 1981 and were therefore not registered in the Danish Population's Education Register. Data on residence and annual personal income were missing by less than 0.1%.

In a sensitivity analysis of the adjustment for SES (online supplemental table 1), adjustment for the highest attained education compared with adjustment for both the highest attained education and annual personal income overall resulted in the same estimates. Therefore, income was omitted and only education was used in the analyses to adjust for the confounding potential of SES.

Psychiatric morbidity

Table 2 lists the prevalence of hospital-treated psychiatric disorders in participants and non-participants registered

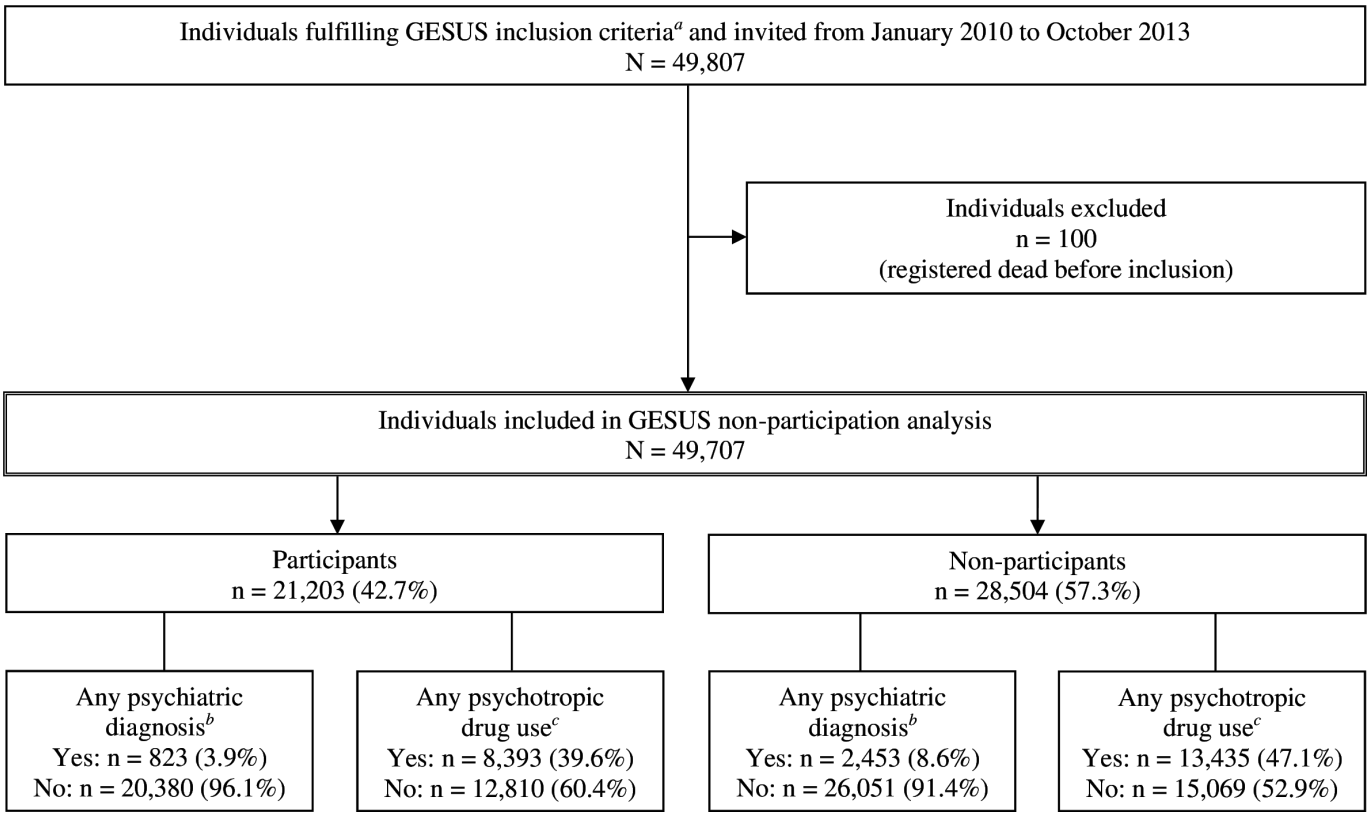

Figure 1 Flow diagram of GESUS inclusion and non-participation analysis. GESUS, the Danish General Suburban Population Study. [a]GESUS inclusion criteria: (1) Danish citizenship, (2) a Danish Civil Registration number, (3) a registered address in Naestved Municipality (postal codes: DK-4160, DK-4171, DK-4250, DK-4262, DK-4684, DK-4700, DK-4733, DK-4736), (4) ≥20 years of age (all individuals >30 years and a random selection of 25% of the population aged 20–30 years were invited). [b]WHO *International Classification of Diseases* 10th revision (version 2019) Chapter V *Mental and behavioural disorders* (F00–F99). [c]WHO Anatomical Therapeutic Chemical (ATC) code: N05, N06, N07D. ATC code N03AG01 and N03AX09 in the absence of any epilepsy diagnosis.

since 1994. 2453 (8.6%) non-participants had a psychiatric diagnosis at GESUS inclusion compared with 823 (3.9%) participants equivalent to an OR of 1.84 (95% CI 1.69 to 2.00) for non-participation after adjustment for sociodemographic factors. All diagnostic groups—except eating disorders—were associated with non-participation (ORs ranging from 1.01 to 5.76) with the greatest association found in organic mental disorders (F00–F09, OR 5.76 (3.90 to 8.48)), substance abuse (F10–F19, OR 3.12 (2.14 to 4.54)) and psychotic disorders (F20–F29, OR 3.12 (2.33 to 4.18)). Eating disorders (F50–F59) seemed to be associated with participation ($OR_{non\text{-}participation}$ of 0.69 (0.47 to 1.03)).

Onset of psychiatric illness, and illness duration at the time of GESUS inclusion, did not differ between psychiatric non-participants and participants (table 3). Psychiatric patients with illness courses characterised by either three or more psychiatric acute clinic visits (age- and sex-adjusted OR 1.42 (1.05 to 1.91)), three or more psychiatric outpatient clinic courses (OR 1.36 (1.06 to 1.74)) or three or more psychiatric hospital admissions (OR 1.71 (1.34 to 2.19)) seemed to participate less than psychiatric patients with fewer hospital contacts. However, an association with non-participation persisted only in psychiatric patients with three or more psychiatric hospital admissions (OR 1.53 (1.19 to 1.97)) after full adjustment for sociodemographic factors. Both the total number of days hospitalised and the time proportion spent hospitalised after illness onset were increased in psychiatric non-participants compared with psychiatric participants (median days hospitalised: 209 vs 185, median time proportion spent hospitalised after illness onset: 9% vs 7.3%).

Table 4 details the use of psychotropic drugs in the GESUS population since 1995. A total of 21 828 (43.9%) GESUS subjects—of whom 2809 (12.9%) subjects also had a registered psychiatric diagnosis—had redeemed at least one prescription for a psychotropic drug before study inclusion. In non-participants, the proportion was 47.1% compared with only 39.6% in participants. The use of any psychotropic drug was found to be associated with non-participation, also after adjusting for co-occurrence of psychiatric diagnoses (OR 1.26 (1.21 to 1.31)). Psychotropic drug groups independently associated with non-participation included antidementia drugs (OR 4.75 (2.71 to 8.34)), drugs used in addictive disorders (OR 1.53 (1.40 to 1.67)), antipsychotics (OR 1.31 (1.20 to 1.43)), antidepressants (OR 1.17 (1.11 to 1.23)) and anxiolytics (OR 1.14 (1.08 to 1.19)). Use of hypnotics and sedatives, mood stabilisers or psychostimulants was

Table 1 Baseline sociodemographic characteristics of participants and non-participants of the GESUS population

	Total (N=49 707)	Participants (n=21 203)	Non-participants (n=28 504)	OR_{crude} (95% CI) for non-participation	$OR_{adjusted}$* (95% CI) for non-participation
Sex					
Female	25 627 (51.6%)	11 562 (54.5%)	14 065 (49.3%)	1 (ref.)	1 (ref.)
Male	24 080 (48.4%)	9641 (45.5%)	14 439 (50.7%)	1.23 (1.19 to 1.28)	1.36 (1.31 to 1.41)
Age groups (years)					
<40	8871 (17.8%)	2973 (14.0%)	5898 (20.7%)	2.26 (2.13 to 2.40)	2.95 (2.76 to 3.15)
40–49	10 972 (22.1%)	4543 (21.4%)	6429 (22.6%)	1.61 (1.53 to 1.70)	2.18 (2.05 to 2.31)
50–59	10 421 (21.0%)	4767 (22.5%)	5654 (19.8%)	1.35 (1.28 to 1.43)	1.71 (1.61 to 1.82)
60–69	10 379 (20.9%)	5527 (26.1%)	4852 (17.0%)	1 (ref.)	1 (ref.)
≥70	9064 (18.2%)	3393 (16.0%)	5671 (19.9%)	1.90 (1.80 to 2.02)	1.24 (1.16 to 1.32)
Country of origin					
Nordic countries†	48 572 (97.7%)	20 766 (97.9%)	27 806 (97.6%)	1 (ref.)	1 (ref.)
Other countries	1135 (2.3%)	437 (2.1%)	698 (2.4%)	1.19 (1.06 to 1.35)	1.12 (0.98 to 1.27)
Residence‡§					
Suburban	30 837 (62.0%)	13 614 (64.2%)	17 233 (60.4%)	1 (ref.)	1 (ref.)
Rural	18 868 (38.0%)	7588 (35.8%)	11 280 (39.6%)	1.18 (1.13 to 1.22)	1.20 (1.15 to 1.25)
Marital status					
Married/reg. partnership	28 285 (56.9%)	14 187 (66.9%)	14 098 (49.5%)	1 (ref.)	1 (ref.)
Widowed/surviving partner	4555 (9.2%)	1715 (8.1%)	2840 (10.0%)	1.67 (1.56 to 1.78)	1.78 (1.65 to 1.92)
Divorced/term. Partnership	6868 (13.8%)	2586 (12.2%)	4282 (15.0%)	1.67 (1.58 to 1.76)	1.66 (1.57 to 1.75)
Unmarried	8181 (16.5%)	2478 (11.7%)	5703 (20.0%)	2.32 (2.20 to 2.44)	1.71 (1.62 to 1.81)
Unknown¶	1818 (3.7%)	237 (1.1%)	1581 (5.5%)	6.71 (5.84 to 7.71)	5.97 (5.17 to 6.90)
Highest attained education					
Basic	14 966 (30.1%)	4883 (23.0%)	10 083 (35.4%)	2.29 (2.16–2.42)	1.81 (1.70 to 1.93)
Upper secondary	1519 (3.1%)	618 (2.9%)	901 (3.2%)	1.62 (1.44 to 1.81)	1.17 (1.04 to 1.32)
Vocational training	22 577 (45.4%)	10 485 (49.5%)	12 092 (42.4%)	1.28 (1.21 to 1.35)	1.08 (1.02 to 1.14)
Bachelor	7760 (15.6%)	4079 (19.2%)	3681 (12.9%)	1 (ref.)	1 (ref.)
Higher education	1888 (3.8%)	936 (4.4%)	952 (3.3%)	1.13 (1.02 to 1.25)	1.18 (1.06 to 1.31)
Unknown**	997 (2.0%)	202 (1.0%)	795 (2.8%)	4.36 (3.71 to 5.12)	2.84 (2.40 to 3.36)
Total personal income (DKK/year)§					
1st quartile	12 362 (25.0%)	4646 (21.9%)	7716 (27.1%)	1.63 (1.55 to 1.71)	1.77 (1.66 to 1.89)
2nd quartile	12 445 (25.0%)	4578 (21.6%)	7867 (27.6%)	1.68 (1.60 to 1.77)	1.59 (1.50 to 1.69)
3rd quartile	12 450 (25.0%)	5816 (27.4%)	6634 (23.3%)	1.12 (1.06 to 1.18)	1.09 (1.03 to 1.15)
4th quartile	12 449 (25.0%)	6163 (29.1%)	6286 (22.1%)	1 (ref.)	1 (ref.)

Values are expressed as number (%). Data were obtained from the Danish Civil Register, the Danish Population's Education Register and the Danish Income Statistics Register.
*Adjusted for all other variables in the table.
†Nordic countries: Denmark, Norway, Sweden, Finland, Greenland, Iceland, Faroe Islands.
‡Suburban: Postal code DK-4700. Rural: Postal codes DK-4160, DK-4171, DK-4250, DK-4262, DK-4684, DK-4733, DK-4736.
§Missing data: Data on residence and annual personal income were missing in less than 0.1%.
¶Dead before extraction of data on marital status from the Danish Civil Register.
**Finished education before 1981 (the Danish Population's Education Register was initiated in 1981).
DKK, Danish krone; GESUS, the Danish General Suburban Population Study.

not independently associated with non-participation. A total of 15 021 (30.2%) GESUS subjects—of whom 5466 (36.4%) participated and 9555 (63.6%) did not participate—had redeemed three or more prescriptions for any psychotropic drug before study inclusion and thus fulfilled our proxy diagnosis of psychiatric illness. This resulted in a total of 15 479 GESUS subjects with an indication of psychiatric morbidity equivalent to 31.1% of the whole GESUS population.

Survival data

In both non-psychiatric and psychiatric participants and non-participants, less than 5% of deaths in the follow-up period were due to unnatural causes (suicide, accidents, violence).

Table 2 The association between hospital-acquired psychiatric diagnoses (since 1994) and non-participation in the GESUS population

	Total (N=49 707)	Participants (n=21 203)	Non-participants (n=28 504)	OR_{crude} (95% CI) for non-participation	$OR_{adjusted}$* (95% CI) for non-participation	$OR_{adjusted}$† (95% CI) for non-participation
Any psychiatric diagnosis						
No	46 431 (93.4%)	20 380 (96.1%)	26 051 (91.4%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	3276 (6.6%)	823 (3.9%)	2453 (8.6%)	2.33 (2.15 to 2.53)	2.28 (2.10 to 2.48)	1.84 (1.69 to 2.00)
Psychiatric diagnostic group‡						
F00–F09 Organic mental disorders	349 (0.7%)	29 (0.1%)	320 (1.1%)	8.63 (6.01 to 12.9)	8.19 (5.59 to 12.0)	5.76 (3.90 to 8.48)
F10–F19 Mental disorders due to substance use	200 (0.4%)	35 (0.2%)	165 (0.6%)	3.69 (2.59 to 5.40)	3.82 (2.64 to 5.51)	3.12 (2.14 to 4.54)
F20–F29 Schizophrenia and related disorders	369 (0.7%)	56 (0.3%)	313 (1.1%)	4.37 (3.32 to 5.87)	4.46 (3.35 to 5.94)	3.12 (2.33 to 4.18)
F30–F39 Mood disorders	1017 (2.0%)	305 (1.4%)	712 (2.5%)	1.83 (1.60 to 2.09)	1.85 (1.61 to 2.12)	1.61 (1.40 to 1.86)
F30–F31 Manic episode and bipolar disorder	136 (0.3%)	45 (0.2%)	91 (0.3%)	1.58 (1.11 to 2.28)	1.69 (1.18 to 2.42)	1.48 (1.02 to 2.15)
F32 Depressive episode	435 (0.9%)	138 (0.7%)	297 (1.0%)	1.68 (1.38 to 2.07)	1.67 (1.36 to 2.05)	1.46 (1.18 to 1.80)
F33 Recurrent depressive disorder	407 (0.8%)	111 (0.5%)	296 (1.0%)	2.09 (1.68 to 2.61)	2.13 (1.71 to 2.66)	1.87 (1.49 to 2.34)
F34–F39 Other mood disorders	39 (0.1%)	11 (0.1%)	28 (0.1%)	1.99 (1.02 to 4.18)	1.91 (0.95 to 3.86)	1.51 (0.73 to 3.11)
F40–F48 Neurotic and stress-related disorders	950 (1.9%)	285 (1.3%)	665 (2.3%)	1.83 (1.59 to 2.10)	1.74 (1.51 to 2.01)	1.47 (1.27 to 1.70)
F50–F59 Eating disorders	103 (0.2%)	53 (0.2%)	50 (0.2%)	0.74 (0.50 to 1.09)	0.66 (0.45 to 0.98)	0.69 (0.47 to 1.03)
F60–F69 Personality disorders	124 (0.2%)	31 (0.1%)	93 (0.3%)	2.35 (1.58 to 3.58)	2.19 (1.45 to 3.30)	1.71 (1.12 to 2.60)
F70–F79 Mental retardation	48 (0.1%)	4 (0.0%)	44 (0.2%)	8.61 (3.49 to 28.6)	7.94 (2.85 to 22.2)	3.29 (1.18 to 9.21)
F80–F89 Developmental disorders	24 (0.0%)	<4 (0.0%)	22 (0.1%)	8.61 (2.54 to 53.7)	6.96 (1.63 to 29.7)	3.02 (0.71 to 12.9)
F90–F98 Behavioural and emotional disorders	45 (0.1%)	4 (0.0%)	41 (0.1%)	8.02 (3.24 to 26.7)	5.93 (2.12 to 16.6)	3.62 (1.28 to 10.3)
F99–F99 Unspecified mental disorder	47 (0.1%)	4 (0.0%)	28 (0.1%)	1.15 (0.65 to 2.10)	1.21 (0.67 to 2.17)	1.01 (0.55 to 1.84)

Values are expressed as number (%). Estimates are expressed as ORs and 95% CIs. Data were obtained from the Danish Psychiatric Central Research Register containing data on all psychiatric hospital contacts with associated psychiatric ICD-10 diagnoses (implemented in Denmark in 1994).
*Adjusted for sex and age.
†Adjusted for sex, age, country of origin, residence, marital status and highest attained education.
‡A single main psychiatric diagnosis for each subject was defined as the numeric lowest registered WHO ICD-10 diagnostic code before GESUS invitation. ICD-10 F10–F19 diagnoses were only defined as the main psychiatric diagnosis if no other psychiatric diagnoses were registered.
GESUS, the Danish General Suburban Population Study; ICD-10, International Classification of Diseases 10th revision (version 2019).

Table 3 The association between psychiatric illness course characteristics and non-participation in invited GESUS subjects with psychiatric diagnoses

	Total subjects with any psychiatric diagnosis (N=3276)	Participants with any psychiatric diagnosis (n=823)	Non-participants with any psychiatric diagnosis (n=2453)	OR_{crude} (95% CI) for non-participation	$OR_{adjusted}$* (95% CI) for non-participation	$OR_{adjusted}$† (95% CI) for non-participation
Age of onset (years)	41.9 (31.6, 54.2)	42.6 (32.8, 52.6)	41.8 (31.4, 54.8)			
Illness duration (years)	7.7 (3.8, 13.0)	7.2 (3.7, 12.6)	7.9 (3.9, 13.1)			
Psychiatric outpatient clinic courses						
0	650 (19.8%)	171 (20.8%)	479 (19.5%)	1 (ref.)	1 (ref.)	1 (ref.)
1–2	1828 (55.8%)	483 (58.7%)	1345 (54.8%)	0.99 (0.81 to 1.22)	0.96 (0.78 to 1.18)	0.91 (0.73 to 1.13)
≥3	798 (24.4%)	169 (20.5%)	629 (25.6%)	1.33 (1.04 to 1.70)	1.36 (1.06 to 1.74)	1.13 (0.88 to 1.47)
Psychiatric acute clinic visits						
0	1969 (60.1%)	481 (58.4%)	1488 (60.7%)	1 (ref.)	1 (ref.)	1 (ref.)
1–2	997 (30.4%)	279 (33.9%)	718 (29.3%)	0.83 (0.70 to 0.99)	0.87 (0.73 to 1.03)	0.85 (0.71 to 1.02)
≥3	310 (9.5%)	63 (7.7%)	247 (10.1%)	1.27 (0.94 to 1.70)	1.42 (1.05 to 1.91)	1.28 (0.94 to 1.74)
Psychiatric hospital admissions						
0	1878 (57.3%)	507 (61.6%)	1371 (55.9%)	1 (ref.)	1 (ref.)	1 (ref.)
1–2	887 (27.1%)	217 (26.4%)	670 (27.3%)	1.14 (0.95 to 1.37)	1.21 (1.00 to 1.46)	1.14 (0.94 to 1.39)
≥3	511 (15.6%)	99 (12.0%)	412 (16.8%)	1.54 (1.21 to 1.96)	1.71 (1.34 to 2.19)	1.53 (1.19 to 1.97)
Cumulative days hospitalised (days)	202 (19, 588)	185 (17, 442)	209 (19, 652)			
Time spent hospitalised after onset (%)	8.5 (0.7, 31.5)	7.3 (0.7, 23.0)	9.0 (0.7, 34.5)			

Values are expressed as number (%) or median (IQR). Estimates are expressed as ORs and 95% CIs. Data were obtained from the Danish Psychiatric Central Research Register.
*Adjusted for sex and age.
†Adjusted for sex, age, country of origin, residence, marital status and highest attained education.
GESUS, the Danish General Suburban Population Study.

Table 4 The association between psychotropic drug use (since 1995) and non-participation in the GESUS population

	Total (N=49 707)	Participants (n=21 203)	Non-participants (n=28 504)	OR_{crude} (95% CI) for non-participation	$OR_{adjusted}$ (95% CI) for non-participation	$OR_{adjusted}$ (95% CI) for non-participation
Any psychotropic drug use						
No	27 879 (56.1%)	12 810 (60.4%)	15 069 (52.9%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	21 828 (43.9%)	8393 (39.6%)	13 435 (47.1%)	1.36 (1.31 to 1.41)	1.38 (1.32 to 1.43)*	1.26 (1.21 to 1.31)†
Antipsychotics						
No	46 298 (93.1%)	20 231 (95.4%)	26 067 (91.5%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	3409 (6.9%)	972 (4.6%)	2437 (8.5%)	1.95 (1.80 to 2.10)	1.53 (1.40 to 1.66)‡	1.31 (1.20 to 1.43)§
Anxiolytics						
No	37 594 (75.6%)	16 697 (78.7%)	20 897 (73.3%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	12 113 (24.4%)	4506 (21.3%)	7607 (26.7%)	1.35 (1.29 to 1.41)	1.21 (1.15 to 1.27)‡	1.14 (1.08 to 1.19)§
Hypnotics and sedatives						
No	39 218 (78.9%)	17 124 (80.8%)	22 094 (77.5%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	10 489 (21.1%)	4079 (19.2%)	6410 (22.5%)	1.22 (1.17 to 1.27)	1.06 (1.00 to 1.11)‡	1.04 (0.99 to 1.10)§
Antidepressants						
No	37 683 (75.8%)	16 861 (79.5%)	20 822 (73.0%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	12 024 (24.2%)	4342 (20.5%)	7682 (27.0%)	1.43 (1.37 to 1.49)	1.22 (1.16 to 1.28)‡	1.17 (1.11 to 1.23)§
Mood stabilisers						
No	48 869 (98.3%)	20 917 (98.7%)	27 952 (98.1%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	838 (1.7%)	286 (1.3%)	552 (1.9%)	1.44 (1.25 to 1.67)	0.95 (0.81 to 1.10)‡	1.00 (0.86 to 1.17)§
Psychostimulants						
No	49 444 (99.5%)	21 122 (99.6%)	28 322 (99.4%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	263 (0.5%)	81 (0.4%)	182 (0.6%)	1.68 (1.29 to 2.18)	1.06 (0.81 to 1.39)‡	0.96 (0.72 to 1.27)§
Antidementia drugs						
No	49 553 (99.7%)	21 189 (99.9%)	28 364 (99.5%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	154 (0.3%)	14 (0.1%)	140 (0.5%)	7.47 (4.31 to 12.9)	5.63 (3.23 to 9.80)‡	4.75 (2.71 to 8.34)§
Drugs used in addictive disorders						
No	46 862 (94.3%)	20 393 (96.2%)	26 469 (92.9%)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	2845 (5.7%)	810 (3.8%)	2035 (7.1%)	1.94 (1.78 to 2.10)	1.66 (1.52 to 1.81)‡	1.53 (1.40 to 1.67)§

Values are expressed as number (%). Estimates are expressed as ORs and 95% CIs. Data were obtained from the Danish National Prescription Registry containing data on every redeemed prescription from any Danish community pharmacy since 1995.
Antipsychotics: WHO Anatomical Therapeutic Chemical (ATC) code N05A (except lithium, N05AN). Anxiolytics: ATC code N05B. Hypnotics and sedatives: ATC code N05C. Antidepressants: ATC code N06A. Mood stabilisers: ATC code N05AN (lithium), N03AG01 (valproic acid), N03AX09 (lamotrigine). Psychostimulants: ATC code N06B. Antidementia drugs: ATC code N06D. Drugs used in addictive disorders: ATC code N07B.
*Adjusted for sex, age and the presence of any psychiatric diagnosis.
†Adjusted for sex, age, country of origin, residence, marital status, highest attained education and the presence of any psychiatric diagnosis.
‡Adjusted for sex, age and the use of psychotropic drugs from any of the other included drug groups.
§Adjusted for sex, age, country of origin, residence, marital status, highest attained education and the use of psychotropic drugs from any of the other included drug groups.
GESUS, the Danish General Suburban Population Study.

Figure 2A shows Kaplan-Meier-estimated survival curves in a 5-year follow-up after GESUS invitation, stratified by participation status and psychiatric morbidity. The 5-year survival probability was highest in non-psychiatric participants (97.5% (95% CI 97.2 to 97.7)), followed by psychiatric participants (95.5% (94.9 to 96.0)), non-psychiatric non-participants (92.6% (92.2 to 93.0)) and lowest in psychiatric non-participants (81.1% (80.4 to 81.9)) (log-rank test: p<0.0001). Cumulative incidence functions of MACE in the 5-year follow-up period are shown in figure 2B. Incidences of MACE also differed by participation status and psychiatric morbidity (Gray's test: p<0.0001) with the highest registered incidence in psychiatric non-participants (12.2% (95% CI 11.5 to 12.8) and the lowest incidence in non-psychiatric participants (3.5% (3.2 to 3.8)) (psychiatric participants: 6.0% (5.4 to 6.7); non-psychiatric non-participants: 6.1 (5.8 to 6.5)).

Overall, GESUS non-participants had increased rates of both all-cause mortality (HR 2.53 (95% CI 2.32 to 2.76)) and MACE (HR 1.69 (95% CI 1.56 to 1.84)) relative to GESUS participants (ref.) (table 5). Likewise, individuals with psychiatric morbidity had higher rates of all-cause mortality (HR 1.52 (95% CI 1.42 to 1.62)) and MACE (HR 1.45 (1.35 to 1.55)) compared with individuals without psychiatric morbidity (ref.). Stratification by both participation and psychiatric morbidity status showed the same trend as presented in figure 2; compared with

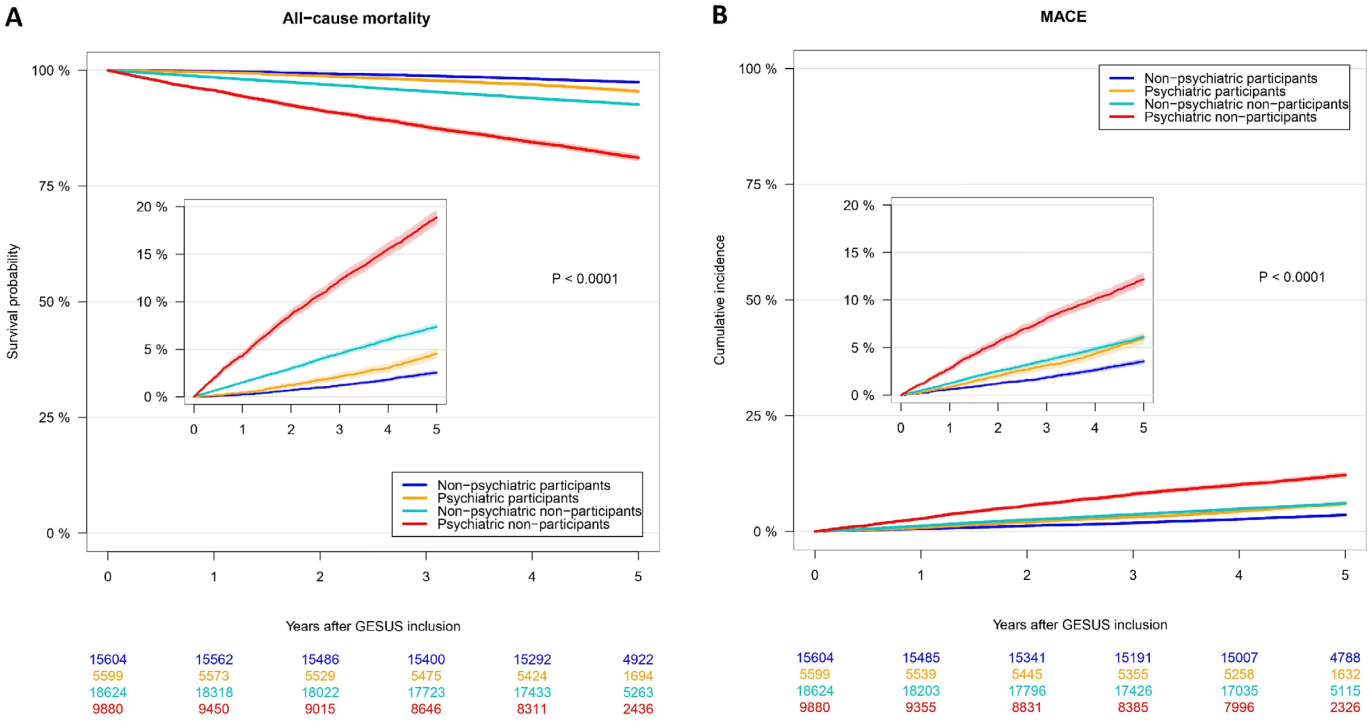

Figure 2 All-cause mortality and MACEs in the GESUS population (5-year follow-up). (A) Kaplan-Meier survival curve with 95% CIs for all-cause mortality and the cumulative incidence of all-cause mortality. (B) The cumulative incidence of MACEs with 95% CI. Data were obtained from the Danish Register of Causes of Death and the Danish National Patient Registry. GESUS, the Danish General Suburban Population Study; MACE, major adverse cardiovascular event.

non-psychiatric participants (ref.), the rates of all-cause mortality and MACE were most increased in psychiatric non-participants (HR 3.37 (95% CI 3.01 to 3.78) and 2.30 (2.07 to 2.56), respectively), followed by non-psychiatric non-participants (HR 2.26 (2.02 to 2.54) and 1.65 (1.48 to 1.83), respectively) and psychiatric participants (HR 1.23 (1.05 to 1.44) and 1.39 (1.21 to 1.59), respectively). The association between psychiatric morbidity and (1) all-cause mortality and (2) MACE was altered depending on participation status, indicating an interaction between psychiatric morbidity and participation status (likelihood ratio test: p<0.0001 (for both outcomes)).

In a hypothetical cohort consisting of the complete GESUS population (N=49 707) minus the subpopulation of psychiatric non-participants (n=39 827), the estimated all-cause mortality and MACE incidence rates were 10.4 (95% CI 10.0 to 10.9) and 10.6 (10.2 to 11.1) per 1000 person-years, respectively. In comparison, the incidence rate estimates of all-cause mortality and MACE of the complete GESUS population (N=49 707)—including all subpopulations both participants and non-participations—were 16.3 (15.8 to 16.8) and 13.8 (13.3 to 14.3) per 1000 person-years (table 5, online supplemental table 2).

DISCUSSION

Participation bias in many aspects of society's activities is generally assumed, but scientific evidence and quantitative estimates are limited. This is to our knowledge the largest study to describe non-participation bias due to psychiatric illness in a general population survey and the first study to investigate the potential impact of psychiatric non-participation on population survey estimates of somatic health. In this study, we report a prevalence of severe psychiatric disorders more than twice as high in non-participants compared with participants in GESUS, as well as a more severe psychiatric illness course in non-participating compared with participating psychiatric patients. All psychiatric ICD-10 diagnoses—except eating disorders—were associated with non-participation, and psychiatric disorders particularly under-represented among study participants were psychotic disorders, substance abuse and dementia. The prevalence of individuals using psychotropic drugs was higher among non-participants, and antipsychotics, antidementia drugs and drugs used in addictive disorders were the most strongly associated with non-participation. Moreover, we report that even after adjustment for sociodemographic factors, non-participants with psychiatric morbidity had a twice as high rate of MACE and a more than three times higher rate of death than participants without psychiatric morbidity. In a hypothetical GESUS cohort including both participants and non-participants except the subpopulation of psychiatric non-participants, incidence rates of all-cause mortality and MACE were lower compared with incidence rates estimated from the complete GESUS population of all invited individuals. Thus, the GESUS population cohort—comprised of the GESUS participants only—underestimates MACE and the total mortality due to non-participation bias in general,

Table 5 Five-year all-cause mortality and MACEs according to GESUS participation and psychiatric morbidity

	All-cause mortality				MACE			
	IR (95% CI)	HR_{crude} (95% CI)	$HR_{adjusted}$* (95% CI)	$HR_{adjusted}$† (95% CI)	IR (95% CI)	HR_{crude} (95% CI)	$HR_{adjusted}$* (95% CI)	$HR_{adjusted}$† (95% CI)
The total GESUS population	16.3 (15.8 to 16.8)				13.8 (13.3 to 14.3)			
By participation status								
Participants	6.2 (5.7 to 6.7)	1 (ref.)	1 (ref.)	1 (ref.)	8.6 (8.1 to 9.2)	1 (ref.)	1 (ref.)	1 (ref.)
Non-participants	24.2 (23.3 to 25.0)	3.90 (3.59 to 4.25)	4.16 (3.83 to 4.53)	2.53 (2.32 to 2.76)	17.8 (17.1 to 18.6)	2.07 (1.92 to 2.24)	2.23 (2.06 to 2.41)	1.69 (1.56 to 1.84)
By psychiatric diagnosis								
Non-psychiatric subjects	10.6 (10.1 to 11.1)	1 (ref.)	1 (ref.)	1 (ref.)	10.3 (9.8 to 10.8)	1 (ref.)	1 (ref.)	1 (ref.)
Psychiatric subjects	29.4 (28.2 to 30.7)	2.78 (2.61 to 2.96)	2.05 (1.92 to 2.19)	1.52 (1.42 to 1.62)	21.9 (20.8 to 23.1)	2.13 (1.99 to 2.29)	1.70 (1.59 to 1.83)	1.45 (1.35 to 1.55)
By participation and psychiatric diagnosis								
Non-psychiatric participants	5.1 (4.6 to 5.6)	1 (ref.)	1 (ref.)	1 (ref.)	7.2 (6.6 to 7.9)	1 (ref.)	1 (ref.)	1 (ref.)
Psychiatric participants	9.3 (8.1 to 10.5)	1.81 (1.55 to 2.12)	1.42 (1.21 to 1.66)	1.23 (1.05 to 1.44)	12.5 (11.2 to 14.0)	1.74 (1.52 to 1.99)	1.45 (1.27 to 1.66)	1.39 (1.21 to 1.59)
Non-psychiatric non-participants	15.4 (14.6 to 16.2)	3.01 (2.69 to 3.36)	3.42 (3.06 to 3.83)	2.26 (2.02 to 2.54)	12.9 (12.2 to 13.7)	1.79 (1.62 to 1.98)	2.03 (1.83 to 2.24)	1.65 (1.48 to 1.83)
Psychiatric non-participants	42.0 (40.1 to 43.9)	8.23 (7.38 to 9.17)	6.64 (5.95 to 7.41)	3.37 (3.01 to 3.78)	27.8 (26.2 to 29.4)	3.85 (3.48 to 4.26)	3.33 (3.00 to 3.69)	2.30 (2.07 to 2.56)

Cox proportional hazards regression analysis. Data were obtained from the Danish Register of Causes of Death and the Danish National Patient Registry.
*Adjusted for age and sex.
†Adjusted for sex, age, country of origin, residence, marital status and highest attained education.
GESUS, the Danish General Suburban Population Study; IR, incidence rate (events per 1000 person-years); MACE, major adverse cardiovascular event.

and psychiatric non-participation in particular. In future studies, this bias can be minimised by various statistical methods, for example, stratification, matching, propensity score matching and inverse probability weighting.

The increased somatic morbidity and mortality in individuals with psychiatric illness are well-established,[6–12] but the demonstration of a twofold incidence of MACE and a 14% reduced survival probability (predominantly due to death of natural causes) in non-participants with psychiatric illness compared with participants with psychiatric illness has not been described before. Our findings indicate that not only do psychiatric patients participate less frequently in population studies, but the group of participating psychiatric patients is also not representative of the overall psychiatric population in terms of either psychiatric diagnostic group, psychiatric illness severity, somatic comorbidity or all-cause mortality. One could hypothesise that participation in health studies—independently of the presence of psychiatric morbidity—is associated with better health behaviour, overall resulting in both more well-treated psychiatric disorders and somatic diseases. Our results also imply that population surveys aiming at determining psychiatric and somatic disease prevalence may underestimate the true burden, and survey subgroup analyses of specific psychiatric diagnostic groups—especially those with low participation rate (psychotic disorders, substance abuse, dementia)—constitute a great challenge as they may be inaccurate due to group heterogenicity and non-representative responders.

Our finding of an association between psychiatric disorders and non-participation in population studies was consistent with that of previous studies.[15 18–23] Across all studies, a previous hospital-registered diagnosis of schizophrenia or substance abuse was most strongly associated with non-participation (no other studies included diagnoses of dementia).[18 19 22] However, the association between mood disorders and non-participation was inconsistent, perhaps due to different study purposes or demands.[18 20–22] The prevalence of individuals with hospital-treated psychiatric disorders was markedly higher in GESUS (8.6% in non-participants, 3.9% in participants) compared with other studies (4.2%–5.1% in non-participants, 2.0%–2.5% in participants),[18–20] which may be explained by a biased difference due to inclusion of specific age groups or specific psychiatric diagnoses or a true difference related to sociodemographic variations. After including psychotropic drug use in the definition of psychiatric morbidity, the prevalence of psychiatric morbidity in GESUS increased to 31.1%, like the findings of Jensen *et al*.[22]

Limitations of our study include the lack of registry data on psychiatric diagnoses in primary care. Although we tried to accommodate by including psychotropic drug use as a proxy measure of psychiatric illness, this still leaves mentally ill individuals without pharmacological or specialty psychiatric treatment unidentified. We only included the primary diagnosis in the definition and description of psychiatric illness, and we cannot rule out that the presence of psychiatric comorbidities (particularly substance abuse) would be associated with even higher rates of excess morbidity and mortality. Another challenge is the registry-based qualitative description of psychiatric illness. However, in line with previous studies,[22 33 34] we included the cumulative use of psychiatric hospital services and time spent in inpatient care as proxy measures of illness severity and chronicity, although these are not necessarily correlated. We adjusted estimates for sociodemographic factors well-known to be determinants of non-participation,[13–17] but due to the close relation between psychiatric morbidity and sociodemographic factors,[35] this might have diluted the true associations, just as we cannot exclude residual confounding. It is also likely that the GESUS participation rate and pattern were affected by the study purpose and demands, which were more extensive than demands of most previous population studies evaluating mental health bias,[15 18–23] perhaps leading to a lower participation rate (43%). The possible effect of this aspect on the differential participation of individuals with psychiatric illnesses is difficult to evaluate and thus unknown. Although a wide age range was included in GESUS, only 25% of individuals aged 20–30 years were invited, possibly leading to a slight underestimation of the early-onset psychiatric disorders. It should also be considered that GESUS was conducted in a suburban and rural population, potentially limiting the extrapolation to populations of other sociodemographic compositions.

To conclude, this is to our knowledge the first study to investigate the impact of psychiatric non-participation on population survey estimates of somatic health. By unique access to data on both study participants and non-participants enabled by cross-linkage to Danish nationwide registries, we demonstrate considerable non-participation bias in a large general population study by under-representation of psychiatric patients leading to distorted estimates of both psychiatric and somatic morbidity prevalence and severity as well as all-cause mortality. To obtain accurate estimates from future population studies to use for strategies in public health efforts—particularly those aimed at psychiatric conditions—initiatives are necessary. We suggest considering the following: optimisation of recruitment strategies specifically targeting individuals with psychiatric illness and use of statistical sampling weights[36] to adjust for differences between sample and background population, particularly focusing on the representation of psychiatric illnesses.

Contributors CE, HEP and AJ designed the study. ZR, MR, AJ and HEP performed the data preparation. ZR, AJ, HEP and CT-P performed the analyses. ZR wrote the first draft of the manuscript and all authors contributed to and approved the final version. As guarantors, AJ and ZR accepted full responsibility for the work and the conduct of the study, had access to all data and controlled the decision to publish. The corresponding author, AJ, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval GESUS was approved by the appropriate institutional review boards and ethical committees (SJ-113, SJ-114, SJ-147, SJ-278) and was reported to the Danish Data Protection Agency (REG-27–2015, REG-103–2018, 2008-58-0028). All participants gave written informed consent after receiving a complete description of the study. The conduction of GESUS follows the principles of the Declaration of Helsinki. In Denmark, registry-based research studies do not require specific consent or ethical approval, only data approval from the Danish Data Protection Agency.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. All data are housed at secured servers at Statistics Denmark with encrypted personal registration numbers. Aggregated data can be exported from Statistics Denmark but not individual data. Access to the study data is only allowed to foreign researchers with an affiliation to a recognised Danish research organisation.

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