### Supplementary Table 1. Absolute volumes

|  |  |  |
| --- | --- | --- |
| **Region** | **Schizophrenia**  **(n=176)**  **Left (SD) / Right (SD)** | **Healthy volunteer**  **(n=173)**  **Left (SD) / Right (SD)** |
| CA1 | 624 (81) / 655 (97) | 641 (79) / 671 (80) |
| CA3 | 196 (28) / 214 (33) | 201 (27) / 218 (31) |
| CA4 | 245 (28) / 256 (31) | 257 (28) / 263 (29) |
| GC-ML-DG | 288 (34) / 301 (37) | 302 (33) / 309 (34) |
| HATA | 61 (10) / 63 (10) | 62 (10) / 66 (10) |
| Hippocampal tail | 530 (76) / 563 (85) | 557 (71) / 583 (67) |
| Fimbria | 89 (23) / 87 (22) | 92 (20) / 91 (21) |
| Hippocampal fissure | 159 (26) / 160 (26) | 153 (25) / 150 (27) |
| Molecular\_layer\_HP | 563 (66) / 579 (72) | 581 (63) / 592 (61) |
| Parasubiculum | 63 (12) / 60 (11) | 65 (13) / 63 (12) |
| Presubiculum | 319 (44) / 304 (38) | 328 (42) / 311 (40) |
| Subiculum | 439 (55) / 437 (53) | 449 (55) / 443 (49) |
| Hippocampus | 3416 (385) / 3519 (412) | 3536 (369) / 3609 (358) |
| ICV | 1570 (167) | 1586 (153) |

Absolute HF subregion, hippocampal, and ICV volumes by group and hemisphere. The absolute volumes are in mean mm3 (SD) except for ICV which is in mean cm3 (SD).

### Supplementary Table 2. Associations between hippocampal subregion volumes and cognitive domain scores

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Cognitive Domain** | **HF Subregion** | **Beta** | **Standard Error** | **n** | **t-value** | **p-value** |
| Attention/Vigilance | GC-ML-DG | 0.005238 | 0.002788 | 305 | 1.88 | 0.0612 |
| Reasoning/Problem Solving | GC-ML-DG | 0.00437 | 0.002287 | 310 | 1.91 | 0.057 |
| Speed Of Processing | GC-ML-DG | 0.007433 | 0.002311 | 310 | 3.22 | **0.0014** |
| Verbal Learning | GC-ML-DG | 0.00735 | 0.002464 | 311 | 2.98 | 0.0031 |
| Visual Learning | GC-ML-DG | 0.007076 | 0.002212 | 307 | 3.2 | **0.0015** |
| Working Memory | GC-ML-DG | 0.005712 | 0.002281 | 311 | 2.5 | 0.0128 |
| CMINDS Composite | GC-ML-DG | 0.007903 | 0.002605 | 302 | 3.03 | 0.0026 |
|  |  |  |  |  |  |  |
| Attention/Vigilance | CA4 | 0.005834 | 0.003291 | 305 | 1.77 | 0.0773 |
| Reasoning/Problem Solving | CA4 | 0.005497 | 0.002687 | 310 | 2.05 | 0.0416 |
| Speed Of Processing | CA4 | 0.008697 | 0.002717 | 310 | 3.2 | **0.0015** |
| Verbal Learning | CA4 | 0.008751 | 0.002895 | 311 | 3.02 | 0.0027 |
| Visual Learning | CA4 | 0.008687 | 0.002596 | 307 | 3.35 | **0.0009** |
| Working Memory | CA4 | 0.006724 | 0.002681 | 311 | 2.51 | 0.0126 |
| CMINDS Composite | CA4 | 0.00941 | 0.003073 | 302 | 3.06 | 0.0024 |
|  |  |  |  |  |  |  |
| Attention/Vigilance | Molecular Layer | 0.003302 | 0.001534 | 305 | 2.15 | 0.0321 |
| Reasoning/Problem Solving | Molecular Layer | 0.002718 | 0.001262 | 310 | 2.15 | 0.0321 |
| Speed Of Processing | Molecular Layer | 0.003882 | 0.001279 | 310 | 3.03 | 0.0026 |
| Verbal Learning | Molecular Layer | 0.003918 | 0.001364 | 311 | 2.87 | 0.0044 |
| Visual Learning | Molecular Layer | 0.004036 | 0.00122 | 307 | 3.31 | **0.0011** |
| Working Memory | Molecular Layer | 0.002674 | 0.001265 | 311 | 2.11 | 0.0353 |
| CMINDS Composite | Molecular Layer | 0.004575 | 0.001433 | 302 | 3.19 | **0.0016** |
|  |  |  |  |  |  |  |
| Attention/Vigilance | HippocampalTail | 0.004244 | 0.001271 | 305 | 3.34 | **0.0009** |
| Reasoning/Problem Solving | Hippocampal Tail | 0.002011 | 0.001057 | 310 | 1.9 | 0.058 |
| Speed Of Processing | Hippocampal Tail | 0.002414 | 0.001076 | 310 | 2.24 | 0.0256 |
| Verbal Learning | Hippocampal Tail | 0.003231 | 0.001142 | 311 | 2.83 | 0.005 |
| Visual Learning | Hippocampal Tail | 0.003222 | 0.001026 | 307 | 3.14 | 0.0019 |
| Working Memory | Hippocampal Tail | 0.002073 | 0.00106 | 311 | 1.96 | 0.0514 |

P-values < 0.0018 (0.05/7 cognitive domain/4) are presented in bold.

**Supplementary Table 3. Demographics and clinical characteristics for GWA sample**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Schizophrenia  (n=130) | Healthy volunteer  (n=145) | Statistic | p-value |
| Mean age (SD) | 39.0 (11.4) | 38.7 (11.3) | t273=0.23 | 0.81 |
| Gender (M/F) | 107/23 | 103/42 | χ21 =4.83 | 0.03 |
| Handednessa (bilateral/left/right) | 4/10/116 | 2/6/137 | FET | 0.29 |
| Subject socioeconomic statusb (SD) | 4.6 (0.9) | 5.8 (0.9) | t273=-10.30 | <0.0001 |
| Parental socioeconomic statusb (SD) | 5.7 (1.8) | 5.9 (1.5) | t273=-0.55 | 0.58 |
| NAART | 29.4 (12.4) | 40.4 (11.6) | t270= -7.50 | <0.0001 |
| Ethnicity |  |  | FET | 0.46 |
| American Indian or Alaskan Native | 1 | 2 |  |  |
| Asian | 18 | 13 |  |  |
| Black or African American | 22 | 18 |  |  |
| Native Hawaiian or Pacific Islander | 1 | 1 |  |  |
| White | 88 | 111 |  |  |
| Smoking status |  |  | χ22=56.4 | <0.0001 |
| Current smoker | 59 (45%) | 11 (8%) |  |  |
| Ex-smoker | 26 (20%) | 29 (20%) |  |  |
| Never-smoker | 45 (35%) | 105 (72%) |  |  |
| Smoking – current pack-years | 7.43 (13.9) | 2.18 (7.8) | t272=3.91 | < 0.0001 |
| Smoking – lifetime pack-years | 12.12 (17.6) | 2.68 (9.4) | t271=5.61 | < 0.0001 |
| Age at onset | 21.5 (7.0) |  |  |  |
| Duration of illness | 17.5 (11.4) |  |  |  |
| PANSS positive | 15.7 (5.2) |  |  |  |
| PANSS negative | 14.6 (5.4) |  |  |  |
| PANSS general | 28.4 (7.4) |  |  |  |
| PANSS composite | 1.1 (6.5) |  |  |  |

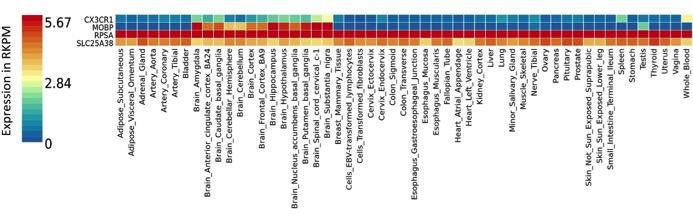
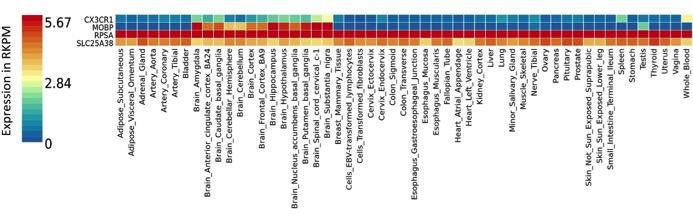
FET=Fisher’s Exact Test; a based on Edinburgh Handedness Inventory [(Oldfield 1971)](https://paperpile.com/c/uAYzme/kTJmH); b based on the Education Level of the Hollingstead Socioeconomic Status Scale [(Hollingshead 1975)](https://paperpile.com/c/uAYzme/61r8Y); NAART = North American Adult Reading Test [(Uttl 2002)](https://paperpile.com/c/uAYzme/wjjvO); PANSS = Positive and Negative Syndrome Scale [(Kay *et al.* 1989)](https://paperpile.com/c/uAYzme/Z0i7T).

### Supplementary Table 4. Top three significant diagnosis by SNP effects

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **rsID** | **CHR** | **BP** | **A1** | **A2** | **MAF** | **P-value** | **B (95% CI)** | **SE** | **r2** |
| rs56055643 | 3 | 39472629 | A | G | 0.40 | 4.8×10−8 | 10.75 (7.0-14.5) | 1.91 | 1 |
| rs7638977 | 3 | 39473101 | T | A | 0.46 | 6.7×10−8 | 10.67 (7.5-15.7) | 1.92 | 0.81 |
| rs2018725 | 3 | 39473224 | T | C | 0.46 | 6.7×10−8 | 10.67 (7.5-15.7) | 1.92 | 0.81 |

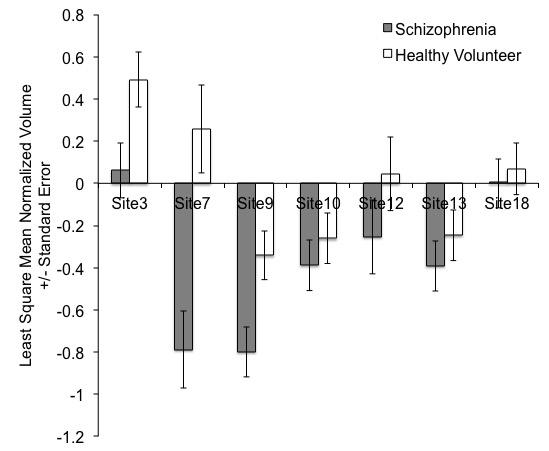
SNP IDs (rsID) for top three significant diagnosis by SNP effects, with chromosome number (CHR), base pair position (BP), minor (A1) and major allele (A2), P-value: p-value of diagnosis by SNP interaction; minor allele frequency (MAF), regression coefficient (B), standard error (SE) and linkage disequilibrium (LD; r2) with rs56055643 (the top SNP).

**Supplementary Figure 1. Gene expression heat map**



Gene expression heat map generated using FUMA’s GENE2FUNC. Average expression per tissue type per gene following winsorization at 50 and log 2 transformation with pseudo count 1. The expression value is presented in RPKM. Cells filled in red represent higher expression compared to cells filled in blue across genes and tissue types. Of note, all four identified genes are expressed in brain tissue.

**Supplementary Figure 2. Normalized dentate gyrus volume by group and site**



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There is a consist pattern of lower dentate gyrus (GC-ML-DG) volume in individuals with schizophrenia compared to control subjects across sites. The least square mean normalized volumes in this figure are based on analysis model 1, controlling for intracranial volume.

### Supplementary introduction (references)

Among these methods, Van Leemput and colleagues’ method [(Van Leemput *et al.* 2008, 2009; Iglesias *et al.* 2013)](https://paperpile.com/c/uAYzme/T0vPJ+DE565+nQ7aR) is implemented in the FreeSurfer [(Fischl *et al.* 2002; Fischl 2012)](https://paperpile.com/c/uAYzme/pE8H+vr4v) morphometry package and has been most widely used in individuals with chronic, first-episode or at ultra-high risk for schizophrenia [(Kühn *et al.* 2012; Francis *et al.* 2013; Mathew *et al.* 2014; Haukvik *et al.* 2015; Kawano *et al.* 2015; Hýža *et al.* 2016; Ho *et al.* 2017a, 2017b; Vargas *et al.* 2017)](https://paperpile.com/c/uAYzme/m1EX+ghD4+ig60+NqTc+GdH5+VnI1+SqBL+I5Xf+pR0V).

### 

### Supplementary methods

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**Participants**

The sample size was based on the ability to adequately model of between scanner effects and included both individuals with schizophrenia and healthy controls at each site [(Glover *et al.* 2012)](https://paperpile.com/c/uAYzme/YuWi9).

### Clinical assessments

Clinical assessments included the Positive and Negative Syndrome Scale (PANSS) [(Kay *et al.* 1989)](https://paperpile.com/c/uAYzme/Z0i7T), the Scale for the Assessment of Positive Symptom (SAPS) [(Andreasen 1984)](https://paperpile.com/c/uAYzme/b6v1I), and the Scale for the Assessment of Negative Symptoms (SANS) [(Andreasen 1983)](https://paperpile.com/c/uAYzme/4SXc9). Socioeconomic status [(Hollingshead 1975)](https://paperpile.com/c/uAYzme/61r8Y), handedness [(Oldfield 1971)](https://paperpile.com/c/uAYzme/kTJmH), basic demographics, and premorbid IQ [(Uttl 2002)](https://paperpile.com/c/uAYzme/wjjvO) were also assessed for all subjects. The raters' assessments were compared with expert ratings. Additional training was provided when raters deviated by more than one point for each item from the expert ratings. Prior to data collection, experienced clinicians were jointly trained on the clinical assessment rating scales with patient interviews. The sample includes 130 paranoid, 6 disorganized, 30 undifferentiated, and 10 residual individuals with schizophrenia. Current antipsychotic medication data were available for 150 of the 176 individuals with schizophrenia (antipsychotics: 130 atypical, 20 typical, and 10 both). Chlorpromazine equivalents (mean±SD=372±390; www.scottwilliamwoods.com/files/Equivtext.doc) could be computed for 144 subjects.

### Image acquisition

High-resolution structural brain scans were acquired on six 3T Siemens TIM® Trio System and one 3T General Electric (GE) Discovery MR750 scanner using standardized sequences, collected between June 2010 and January 2012. Siemens MP-RAGE scan parameters were: TR/TE/TI=2300/2.94/1100ms, flip angle=9°, matrix=256×256x160. GE IR-SPGR scan parameters were: TR/TE/TI=5.95/1.99/450ms, flip angle=12°, matrix=256×256x166. All scans covered the entire brain with FOV=220mm2, voxel size=0.86x0.86x1.2mm, sagittal scan plane, GRAPPA/ASSET acceleration factor=2, and NEX=1. The MRI scanner performance at each site was monitored by acquiring quality assurance data on the FBIRN Phantom [(Friedman & Glover 2006; Friedman *et al.* 2006; Greve *et al.* 2010)](https://paperpile.com/c/uAYzme/h9FKt+fGFqs+PkpOX) during the entire study. Prior to study initiation, a traveling engineer visited each site to review MRI study protocol adherence based on FBIRN’s multi-center imaging study recommendations [(Glover *et al.* 2012)](https://paperpile.com/c/uAYzme/YuWi9).

**Imaging quality control**

FreeSurfer 6.0 HF subregion volumes extraction failed for two out of 185 schizophrenia scans and zero out of 174 healthy volunteer scans. An additional eight scans (seven schizophrenia, one healthy) were eliminated from the analyses based on visual inspection of HF subregion segmentations on sagittal snapshots made using an in-house script that ran FreeSurfer’s freeview, resulting in subregion data for 176 individuals with schizophrenia and 173 healthy volunteers. No manual corrections were performed.

In addition to visual inspections of the images and the hippocampal subregion segmentations, we have run MRIQC [(Esteban *et al.* 2017)](https://paperpile.com/c/uAYzme/dK49) on the images. While the contrast to noise ratio (cnr) for the T1-weighted scans from individuals with schizophrenia was significantly lower than those of healthy volunteers (t311=-2.49, p=0.01), there were no significant correlations between hippocampal subregion volumes and cnr indicating that cnr differences are unlikely to explain the observed differences in volume. To our knowledge, there are no known image quality control metrics that are shown to be associated with hippocampal subregion volumes, though this is a an area of further investigation.

**Genotyping**

Blood samples from each site were sent to the University of California Irvine on dry ice and stored at -80C. DNA extraction from blood samples was performed at the University of California Irvine Genomics High Throughput facility (<http://ghtf.biochem.uci.edu>) between September 2015 and January 2016. DNA was available for 328 subjects. Genotyping of DNA samples from unrelated and mixed ethnicity subjects (schizophrenia=130, healthy volunteers=145; Supplementary Table 3) was successfully performed using the Illumina MEGA+Psych chip (Illumina, SD, USA) between January 2016 - May 2016 at Illumina Genomics Services (San Diego). Genotyping was performed in a single batch which also included samples from other studies. Illumina’s final report showed a sample success rate of 98.13%, locus success rate of 93.36%, and genotype call rate of 99.79%. Data from 5 subjects were eliminated due to poor quality genotyping leaving 323 subjects of which 275 had good quality hippocampal subregion volumes.

**Statistical analysis**

**Correlations with cognitive performance**

We assessed the relationships between DG volumes and cognitive performance, including attention vigilance (schizophrenia=156, healthy volunteers=161), reasoning/problem solving (schizophrenia=161, healthy volunteers=161), speed of processing (schizophrenia=161, healthy volunteers=161), verbal memory (schizophrenia=161, healthy volunteers=162), visual memory (schizophrenia=160, healthy volunteers=159) and working memory (schizophrenia=161, healthy volunteers=162), and CMINDS composite (schizophrenia=155, healthy volunteers=159), in schizophrenia and healthy volunteers using Pearson’s correlations (two-tailed).

**Genome-wide association and gene-based analyses**

GCTA (<http://cnsgenomics.com/software/gcta/#Overview>) overcomes the limitations of the resampling-based methods by calculating p-value for a set of SNPs (±50 Kb of a gene) from an approximated distribution of the sum of χ2-statistics over the SNPs using GWAS summary data of DG volume and linkage disequilibrium (LD) correlations between SNPs from 1000 Genomes Project samples as a reference.

**Gene expression heat mapping**

A gene expression heatmap was created using GENE2FUNC software (<http://fuma.ctglab.nl/tutorial#gene2func>) [(Watanabe *et al.* 2017)](https://paperpile.com/c/uAYzme/2iuq) by averaging expression values per tissue types per gene following reads per kilobase per million (RKPM) winsorization at 50 and log 2 transformation with pseudocount 1.

**Supplementary results**

### Diagnosis effects on intracranial and hippocampal volumes

Patients’ intracranial (LSM±SE=1518±12 cm2) and hippocampal (LSM±SE=3976±34 mm2) volumes were smaller than those of controls (LSM±SE=1549±12 cm2, t333=-2.07, p=<0.05; and LSM±SE=4144±34 mm2, t333=-3.53, p=0.0005, respectively).

**Other clinical variables and possible confounders**

DG volume did not show significant correlations with age at onset, duration of illness, symptom severity, or chlorpromazine equivalent medication dose. Current smoking status, current pack-years, and lifetime pack-years, not surprisingly, differed significantly between patients and controls (Table 1) but also did not show significant correlations with DG volume (p>0.05) or alter the observed group or group × region effects on HF subregion volumes when included as covariates. Analysis of current non-smokers showed significant group [F(1,454)=9.72, p=0.002] and group x region interaction [F(11,447)=2.27, p=0.01] and similar group contrasts for the regional volumes. Analysis of subjects who never smoked also showed significant group [F(1,338)=7.62, p=0.006] and group x region interaction [F(11,329)=2.37, p=0.008] effects.

### Power analysis

Based on the effect sizes, to reject the null-hypothesis of no group differences between schizophrenia and healthy volunteers using a one-tailed test with a threshold of p=0.05, future studies will need 38, 42, 57, 65, 82, 108, 122, 130, 148, 216, and 216 subjects per group to detect volume group differences in the GC-ML-DG, CA4, molecular\_layer\_HP, hippocampal tail, CA1, presubiculum, fimbria, subiculum, HATA, CA3, and parasubiculum, respectively. Our study had 80% power to detect group differences with a Cohen’s d effect size of 0.268 (at p<0.05, one-tailed).

**Abbreviations**

HF = hippocampal formation; DG = dentate gyrus; CA = Cornu Ammonis; GWA = genome-wide association; PANSS = Positive and Negative Syndrome Scale; SAPS = Scale for the Assessment of Positive Symptom; SANS = Scale for the Assessment of Negative Symptoms; molecular\_layer\_HP = molecular layer of the hippocampus; GC-ML-DG = granule cell and molecular cell layer of the DG; HATA = hippocampal-amygdaloid transition region; ICV = intracranial volume; CMINDS = Computerized Multiphasic Interactive Neurocognitive DualDisplay System; SNP = single-nucleotide polymorphism; MAF = minor allele frequency; MDS = multidimensional-scaling; LD = linkage disequilibrium; RKPM = reads per kilobase per million.

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**Supplementary Table 5. STROBE-STREGA Guidelines (reference)**

This report follows the “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Strengthening the REporting of Genetic Association studies” (STREGA) guidelines [(Little *et al.* 2009)](https://paperpile.com/c/uAYzme/ZLXSh) and to the best of our ability has implemented the recommendations listed in the .

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

STREGA extensions are listed in blue.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item No** | **Recommendation** | **Page No** |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 1 |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 4-5 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 6-8 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses  State if the study is the first report of a genetic association, a replication effort, or both (Page No. 8). | 7-8 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 8 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 8 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  Give information on the criteria and methods for selection of subsets of participants from a larger study, when relevant. | 8-9  8-11 |
| (*b*)For matched studies, give matching criteria and the number of controls per case | 8 |
| Variables | 7 | 1. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 2. Clearly define genetic exposures (genetic variants) using a widely-used nomenclature system. Identify variables likely to be associated with population stratification (confounding by ethnic origin). | 8-12  12-13 |
| Data sources/ measurement | 8\* | 1. For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 2. Describe laboratory methods, including source and storage of DNA, genotyping methods and platforms (including he allele calling algorithm used, and its version), error rates and call rates. State the laboratory/center where genotyping aws done. Describe comparability of laboratory methods if there is more than one group. Specify whether genotypes were assigned using all of the data from the study simultaneously or in smaller batches. | 8-12  10,11 |
| Bias | 9 | 1. Describe any efforts to address potential sources of bias 2. For quantitative outcome variables, specify if any investigation of potential bias resulting from pharmacotherapy was undertaken. If relevant, describe the nature and magnitude of the potential bias, and explain what approach was used to deal with this. | 12-16  8, 14, 16, 17, 19 |
| Study size | 10 | Explain how the study size was arrived at  If applicable describe how effects of treatment were dealt with. | 8  8, 14, 16, 17, 19 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 12-14 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 12-15 |
| (*b*) Describe any methods used to examine subgroups and interactions | 12-15 |
| (*c*) Explain how missing data were addressed | 14 |
| (*d*) If applicable, explain how matching of cases and controls was addressed | 8 |
| (*e*) Describe any sensitivity analyses  (f) State whether Hardy-Weinberg equilibrium was considered and, if so, how  (g) Describe any methods used for inferring genotypes or haplotypes  (h) Describe any methods used to assess or address population stratification  (i) Describe and methods used to address multiple comparisons or control risk of false-positive findings  (j) Describe and methods to address and correct for relatedness among subjects | 13-14  10  10  10  14-16  10 |
| **Results** | | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 8-16 |
| (b) Give reasons for non-participation at each stage | 8-16 |
| (c) Consider use of a flow diagram  (d) Report numbers of individuals in whom genotyping was attempted and number of individuals in whom genotyping was successful. | 10,11 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8-9 |
| (b) Indicate number of participants with missing data for each variable of interest | 8-16 |
| Outcome data | 15\* | Report numbers in each exposure category, or summary measures of exposure | 8-16 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Main results | | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 19 |
| (*b*) Report category boundaries when continuous variables were categorized | NA |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period  (d) Report results of any adjustment for multiple comparisons | 13-18 |
| Other analyses | 17 | 1. Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 2. If numerous genetic exposures (genetic variants) were examined, summarize results from all analyses undertaken 3. If detailed results are available elsewhere, state how they can be accessed | | NA  19-20 |
| **Discussion** | | | | |
| Key results | 18 | Summarize key results with reference to study objectives | | 21 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | | 21,22 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | 21,22 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | 21,22 |
| **Other information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | | 23 |

\*Give information separately for cases and controls.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.