

1

1 **Supplementary Online Content**2 **Association of Hyperopia with Incident Clinically Significant Depression:**3 **Epidemiologic and Genetic Evidence in the Middle-aged and Older Population**4 **Supplemental data include 8 tables and 2 figures.**

5 Supplementary Table 1. UK biobank showcase variables used in the paper.

6 Supplementary Table 2. Genetic Association of SNPs with Hyperopia.

7 Supplementary Table 3. Baseline Characteristics Stratified by Incident CSD at Follow-up.

8 Supplementary Table 4. The Sensitivity Analysis Cox Proportional Hazards Models for Incident  
9 CSD by Hyperopia.

10 Supplementary Table 5. Logistic Regression Models for Hyperopia by Hyperopia-PRS Status.

11 Supplementary Table 6. One-sample MR Analysis for the Association between Hyperopia and  
12 CSD using Hyperopia-PRS as the Instrument.13 Supplementary Table 7. Instrument SNPs were used in the MR analysis for the Relationship  
14 Between Hyperopia and major depressive disorder.15 Supplementary Table 8. MR Results for the Relationship Between Hyperopia and major  
16 depressive disorder.

17 Supplementary Figure 1. Histogram of Polygenic Risk Score of Hyperopia.

18 Supplementary Figure 2. Flowchart for population selection for hyperopia from the UK Biobank.

19 This supplementary material has been provided by the authors to give readers additional  
20 information about their work.

2

21 **Supplementary Table 1. UK biobank showcase variables used in the paper.**

| Measure   | Field ID              | Time   | Description   |
|---|-----------------------|--|---|
| <b>Ascertainment of Hyperopia</b>                     |                       |  |   |
| Spherical power (right)                               | 5084                  | Baseline assessment  | the spherical power of refractometry results for the right eye  |
| Spherical power (left)                                | 5085                  | Baseline assessment  | the spherical power of refractometry results for the left eye   |
| Cylindrical power (right)                             | 5087                  | Baseline assessment  | the cylindrical power of refractometry results for the right eye  |
| Cylindrical power (left)                              | 5086                  | Baseline assessment  | the cylindrical power of refractometry results for the left eye   |
| Reason for glasses/contact lenses                     | 6147                  | Baseline assessment  | Touchscreen question "Why were you prescribed glasses/contacts? (You can select more than one answer)".   |
| Ever had cataract                                     | 6148                  | Baseline assessment  | Touchscreen question "Has a doctor told you that you have any of the following problems with your eyes? (You can select more than one answer)".                 |
| Ever had injury or trauma resulting in loss of vision | 6148                  | Baseline assessment  | Touchscreen question "Has a doctor told you that you have any of the following problems with your eyes? (You can select more than one answer)".                 |
| Ever had corneal graft surgery                        | 5328                  | Baseline assessment  | Participants were asked if they had ever had corneal graft surgery  |
| Ever had refractive laser eye surgery                 | 5325                  | Baseline assessment  | Participants were asked if they had refractive laser eye surgery  |
| <b>Ascertainment of Incident CSD</b>                  |                       |  |   |
| Baseline Depression                                   | 20002                 | Baseline assessment  | Self-reported depression.   |
|   | 2050                  |  | Frequency of depressed mood in last 2 weeks   |
|   | 2060                  |  | Frequency of unenthusiasm/disinterest in last 2 weeks   |
| Incident CSD  | 41270 (code F32, F33) | From the date of baseline assessment to either the date of onset CSD, the date of death, or the end of follow-up (28 April 2021) | Hospital in-patient records with CSD as main or any secondary diagnoses based on the 10th edition of the WHO International Classification of Diseases (ICD-10). |
|   | 41280                 |  | The date each ICD-10 diagnosis code was first recorded in either the primary or secondary position in the participant's hospital inpatient records.             |
| <b>Covariates</b>                                     |                       |  |   |
| Age   | 21003                 | Baseline assessment  | Refer to the age of the participant on the day they attended an Assessment Centre, year.  |
| Sex   | 31                    | Baseline assessment  | Sex of participant.   |
| Ethnic background                                     | 21000                 | Baseline assessment  | Recorded as white and non-white.  |

3

|                                     |                         |                     |  |
|-------------------------------------|-------------------------|---------------------|--|
| Townsend deprivation index          | 189                     | Baseline assessment | Townsend deprivation index calculated immediately prior to participant joining UK Biobank based on the preceding national census output areas. Each participant is assigned a score corresponding to the output area in which their postcode is located. |
| Education attainment                | 6138                    | Baseline assessment | Touchscreen question "Which of the following qualifications do you have? (You can select more than one)".  |
| Physical activity levels            | 22036                   | Baseline assessment | Indicates whether a person met the 2017 UK Physical activity guidelines of 150 minutes of walking or moderate activity per week or 75 minutes of vigorous activity.  |
| Smoking status                      | 20116                   | Baseline assessment | This field summarises the current/past smoking status of the participant.  |
| Family history of severe depression | 20107 (code 1,2)        | Baseline assessment | Illnesses of father. Touchscreen question "Has/did your father ever suffer from? (You can select more than one answer)".   |
|                                     | 20110 (code 1,2)        |                     | Illnesses of mother. Touchscreen question "Has/did your mother ever suffer from? (You can select more than one answer)".   |
|                                     | 20111 (code 1,2)        |                     | Illnesses of siblings. Touchscreen question "Have any of your brothers or sisters suffered from any of the following diseases? (You can select more than one answer)".   |
| Hypertension                        | 20002 (code 1065, 1072) | Baseline assessment | Self-reported hypertension.  |
|                                     | 6153 (code 2)           |                     | Use of antihypertensive drugs.   |
|                                     | 4080                    |                     | Average systolic blood pressure of at least 130mmHg.   |
|                                     | 4079                    |                     | Average diastolic blood pressure of at least 80mmHg.   |
| Diabetes mellitus                   | 2443                    | Baseline assessment | Doctor-diagnosed diabetes mellitus. Touchscreen question "Has a doctor ever told you that you have diabetes?"  |
|                                     | 20003                   |                     | The use of anti-hyperglycemic medications.   |
|                                     | 6153 (code 3)           |                     | The use of insulin.  |
|                                     | 30750                   |                     | Glycated hemoglobin level measured by HPLC analysis on a Bio-Rad VARIANT II Turbo ( $\geq 48$ mmol/mol).   |
| Hyperlipidemia                      | 20002 (code 1473)       | Baseline assessment | Self-reported hyperlipidemia.  |
|                                     | 6153                    |                     | The use of statins.  |
|                                     | 20003                   |                     | The use of hyperlipidemia-related medication.  |
|                                     | 30690                   |                     | Blood cholesterol level Measured by CHO-POD analysis on a Beckman Coulter AU5800 ( $\geq 6.21$ mmol/L).  |

22 CSD, clinically significant depression.

4

23 **Supplementary Table 2. Genetic Association of SNPs with Hyperopia.<sup>1</sup>**

| SNP             | CHR | POS       | A1 | A2 | logOR      | SE        | P        |
|-----------------|-----|-----------|----|----|------------|-----------|----------|
| rs12193446      | 6   | 129820038 | G  | A  | 0.213424   | 0.0280639 | 2.85E-14 |
| rs112947941     | 12  | 6997808   | G  | A  | -0.274022  | 0.0376972 | 3.62E-13 |
| rs3138142       | 12  | 56115585  | T  | C  | 0.140075   | 0.0199253 | 2.07E-12 |
| rs4374796       | 6   | 73638262  | C  | C  | 0.124516   | 0.0177213 | 2.12E-12 |
| rs685352        | 15  | 35008335  | G  | A  | -0.123032  | 0.0177938 | 4.70E-12 |
| rs11084579      | 19  | 31802723  | A  | G  | -0.116846  | 0.018753  | 4.64E-10 |
| 8:60179048_CA_C | 8   | 60179048  | C  | CA | 0.114159   | 0.0183887 | 5.37E-10 |
| rs2741297       | 2   | 233387007 | A  | A  | -0.116523  | 0.0195731 | 2.63E-09 |
| rs13380109      | 15  | 79378775  | A  | G  | -0.103178  | 0.0178279 | 7.14E-09 |
| rs2969185       | 17  | 11406081  | A  | C  | -0.0994712 | 0.0176322 | 1.69E-08 |
| rs4794029       | 17  | 47280301  | T  | T  | 0.105089   | 0.0187671 | 2.15E-08 |
| rs1254319       | 14  | 60903757  | A  | G  | -0.104659  | 0.0194532 | 7.45E-08 |
| rs7042950       | 9   | 77149837  | G  | A  | -0.114277  | 0.0213001 | 8.09E-08 |

24 SNP, single-nucleotide polymorphism.

25 <sup>1</sup>Tideman JW, Pärssinen O, Haarman AEG, et al. Evaluation of Shared Genetic Susceptibility to High  
26 and Low Myopia and Hyperopia. *JAMA ophthalmology*. Jun 1 2021;139(6):601-609.

27

5

28 **Supplementary Table 3. Baseline Characteristics Stratified by Incident CSD at**  
 29 **Follow-up.**

| Baseline Characteristics                            | Total          | Sample with no Incident | Sample with   | HR (95% CI) <sup>a</sup> |
|---|----------------|-------------------------|---------------|--------------------------|
|   |                | CSD                     | Incident CSD  |                          |
| N   | 37,179         | 36,605 (98.45)          | 574 (1.54)    | -                        |
| <b>Age, mean (SD), yrs</b>                          | 57.36 (8.12)   | 57.35 (8.12)            | 57.65 (8.14)  | 1.01 (1.00, 1.02)        |
| < 60 y, N (%)                                       | 18,938 (50.94) | 18,649 (50.95)          | 289 (50.35)   | 1 [Reference]            |
| ≥ 60 y, N (%)                                       | 18,241 (49.06) | 17,956 (49.05)          | 285 (49.65)   | 1.05 (0.89, 1.23)        |
| <b>Gender, No. (%)</b>                              |                |                         |               |                          |
| Female  | 19,810 (53.28) | 19,459 (53.16)          | 351 (61.15)   | 1 [Reference]            |
| Male  | 17,369 (46.72) | 17,146 (46.84)          | 223 (38.85)   | <b>0.73 (0.62, 0.86)</b> |
| <b>Ethnicity, No. (%)</b>                           |                |                         |               |                          |
| White   | 33,594 (90.36) | 33,057 (90.31)          | 537 (93.55)   | 1 [Reference]            |
| Non-white   | 3,585 (9.64)   | 3,548 (9.69)            | 37 (6.45)     | 0.65 (0.46, 0.91)        |
| <b>Townsend index, mean (SD)</b>                    | - 1.01 (3.00)  | - 1.02 (3.00)           | - 0.33 (3.18) | <b>1.08 (1.05, 1.11)</b> |
| <b>Education level, No. (%)</b>                     |                |                         |               |                          |
| College or university degree                        | 11,106 (29.87) | 10,985 (30.01)          | 121 (21.08)   | 1 [Reference]            |
| Others  | 26,073 (70.13) | 25,620 (69.99)          | 453 (78.92)   | <b>1.60 (1.30, 1.95)</b> |
| <b>Smoking status, No. (%)</b>                      |                |                         |               |                          |
| Never   | 19,640 (53.29) | 19,388 (53.43)          | 252 (47.48)   | 1 [Reference]            |
| Former/current                                      | 17,218 (46.71) | 16,901 (46.57)          | 317 (55.71)   | <b>1.51 (1.30, 1.79)</b> |
| <b>Family history of severe depression, No. (%)</b> |                |                         |               |                          |
| No  | 32,829 (88.30) | 32,365 (88.42)          | 464 (80.84)   | 1 [Reference]            |
| Yes   | 4,350 (11.70)  | 4,240 (11.58)           | 110 (19.16)   | <b>1.75 (1.42, 2.15)</b> |
| <b>Physical activity, No. (%)</b>                   |                |                         |               |                          |
| Not meeting   | 4,845 (16.21)  | 4,750 (16.14)           | 95 (21.49)    | 1 [Reference]            |

6

## recommendation

|                        |                |                |             |                          |
|------------------------|----------------|----------------|-------------|--------------------------|
| Meeting recommendation | 25,036 (83.79) | 24,689 (83.86) | 347 (78.51) | <b>0.70 (0.55, 0.87)</b> |
|------------------------|----------------|----------------|-------------|--------------------------|

**Visual impairment**

|     |                |                |             |                   |
|-----|----------------|----------------|-------------|-------------------|
| No  | 36,381 (97.97) | 35,821 (97.98) | 560 (97.56) | 1 [ Reference]    |
| Yes | 754 (2.03)     | 740 (2.02)     | 14 (2.44)   | 1.20 (0.70, 2.04) |

**History of diabetes, No.****(%)**

|     |                |                |             |                          |
|-----|----------------|----------------|-------------|--------------------------|
| No  | 34,960 (94.03) | 34,443 (94.07) | 527 (91.81) | 1 [ Reference]           |
| Yes | 2,219 (5.97)   | 2,172 (5.93)   | 47 (8.19)   | <b>1.50 (1.09, 2.00)</b> |

**History of hypertension,****No. (%)**

|     |                |                |             |                   |
|-----|----------------|----------------|-------------|-------------------|
| No  | 9,236 (24.84)  | 9,083 (24.81)  | 153 (26.66) | 1 [ Reference]    |
| Yes | 27,943 (75.16) | 27,522 (75.19) | 421 (73.34) | 1.07 (0.95, 1.22) |

**History of hyperlipidemia,****No. (%)**

|     |                |                |             |                          |
|-----|----------------|----------------|-------------|--------------------------|
| No  | 19,768 (53.17) | 19,477 (53.21) | 291 (50.70) | 1 [ Reference]           |
| Yes | 17,411 (46.83) | 17,128 (46.79) | 283 (49.30) | <b>1.09 (0.91, 1.30)</b> |

30 <sup>a</sup>Note: Cox proportional hazards regression models adjusted for age and gender.

31 CSD, clinically significant depression; No., number; HR, hazard ratio; CI, confidence interval; SD,

32 standard deviation.

33

7

34 **Supplementary Table 4. The Sensitivity Analyses Cox Proportional Hazards**  
 35 **Models for Incident CSD by Hyperopia.**

|  | Multivariable Model |              |
|--|---------------------|--------------|
|  | HR (95% CI)         | P value      |
| <b>Excluding incident of CSD within 2 years</b>                            |                     |              |
| <b>Refractive status</b>   |                     |              |
| Emmetropia   | 1 [Reference]       | -            |
| Myopia   | 1.11 (0.93, 1.32)   | 0.247        |
| Hyperopia  | 1.28 (1.03, 1.60)   | <b>0.015</b> |
| <b>Degrees of hyperopia</b>  |                     |              |
| Emmetropia   | 1 [Reference]       |              |
| Mild hyperopia   | 0.91 (0.55, 1.49)   | 0.701        |
| Moderate hyperopia   | 1.29 (1.01, 1.65)   | <b>0.043</b> |
| High hyperopia   | 1.78 (1.14, 2.76)   | <b>0.011</b> |
| <i>P</i> for trend   |                     | <b>0.005</b> |
| <b>Wearing glasses for hyperopia</b>                                       |                     |              |
| Emmetropia   | 1 [Reference]       |              |
| Wearing hyperopic glasses  | 1.22 (0.92, 1.63)   | 0.172        |
| No hyperopic glasses   | 1.34 (1.02, 1.75)   | <b>0.033</b> |
| <b>Excluding baseline age &lt; 50 years old (n = 7,832)</b>                |                     |              |
| Emmetropia   | 1 [Reference]       |              |
| Hyperopia  | 1.23 (1.03, 1.48)   | <b>0.024</b> |
| <b>Excluding baseline age &lt; 60 years old (n = 18,938)</b>               |                     |              |
| Emmetropia   | 1 [Reference]       |              |
| Hyperopia  | 1.28 (1.03, 1.58)   | <b>0.026</b> |
| <b>Defining baseline depression only using self-report data and ICD-10</b> |                     |              |
| Emmetropia   | 1 [Reference]       |              |
| Hyperopia  | 1.28 (1.04, 1.58)   | <b>0.018</b> |

36 The sensitivity analysis was conducted by excluding incident CSD cases diagnosed within the first year  
 37 of follow-up. The degrees of hyperopia was classified as mild ( $+ 2.00 \text{ D} \leq \text{MSE} < + 3.00 \text{ D}$ ), moderate  
 38 ( $+ 3.00 \text{ D} \leq \text{MSE} < + 4.00 \text{ D}$ ) and high ( $\text{MSE} \geq + 4.00 \text{ D}$ ). Cox proportional hazards regression models  
 39 adjusted for age, gender, ethnicity, smoking status, education level, Townsend index, family history of  
 40 severe depression, physical activity level, visual impairment, the history of hypertension, diabetes and  
 41 hyperlipemia. CSD, clinically significant depression; HR, hazard ratio; CI, confidence interval.

8

42 **Supplementary Table 5. Logistic Regression Models for Hyperopia by**  
 43 **Hyperopia-PRS Status.**

| Hyperopia-PRS status     | Multivariable Model |                  |
|--------------------------|---------------------|------------------|
|                          | OR (95% CI)         | P value          |
| <b>Continue variable</b> | 1.65 (1.50, 1.81)   | <b>&lt;0.001</b> |
| <b>Category variable</b> |                     |                  |
| Low risk                 | 1 [Reference]       | -                |
| Medium risk              | 1.23 (1.16, 1.30)   | <b>&lt;0.001</b> |
| High risk                | 1.43 (1.35, 1.50)   | <b>&lt;0.001</b> |

44 We defined the hyperopia-PRS in thirds: “low risk” (lowest third of hyperopia-PRS), “medium risk”  
 45 (second third), “high risk” (highest third).

46 Logistic regression models adjusted for age, gender, ethnicity, smoking status, education level,  
 47 Townsend index, family history of severe depression, physical activity level, visual impairment, the  
 48 history of hypertension, diabetes and hyperlipemia.

49 PRS, polygenic risk score; OR, odds ratio; CI, confidence interval.



9

50 **Supplementary Table 6. One-sample MR Analysis for the Association between**  
51 **Hyperopia and CSD using Hyperopia-PRS as the Instrument.**

|                      | <b><math>\beta</math> (95% CI)</b> | <b>SE</b> | <b>P value</b> |
|----------------------|------------------------------------|-----------|----------------|
| <b>Hyperopia</b>     | 0.32 (-1.08,1.71)                  | 0.71      | 0.656          |
| <b>Age</b>           | -0.01 (-0.17, 0.01)                | 0.01      | 0.352          |
| <b>Gender (male)</b> | -0.32 (-0.40, -0.26)               | 0.34      | <0.001         |
| <b>Residual</b>      | -0.20 (-1.60, 1.21)                | 0.71      | 0.786          |

52 CSD, clinically significant depression; PRS, polygenetic risk score; MR, mendelian randomization.

53

10

54 **Supplementary Table 7. Instrument SNPs were used in the MR analysis for the**  
55 **Relationship Between Hyperopia and Major Depressive Disorder.**

| SNP                    | A1 | A2 | $\beta$ (SE) for MDD | $\beta$ (SE) for hyperopia |
|------------------------|----|----|----------------------|----------------------------|
| rs11084579             | A  | G  | 0.01                 | -0.12                      |
| rs12193446             | G  | A  | -0.01                | 0.21                       |
| rs13380109             | A  | G  | 0.004                | -0.1                       |
| rs2741297 <sup>†</sup> | T  | C  | -0.01                | -0.12                      |
| rs2969185              | A  | C  | -0.01                | -0.1                       |
| rs3138142              | T  | C  | -0.01                | 0.14                       |
| rs4374796 <sup>†</sup> | T  | G  | 0.01                 | 0.12                       |
| rs4794029              | T  | C  | 0.01                 | 0.11                       |
| rs685352               | G  | A  | -0.003               | -0.12                      |

56 <sup>†</sup>Strand ambiguous SNP. Hence these SNPs were removed in the MR analysis.

57 MR, mendelian randomization; SNP, single-nucleotide polymorphism; SE, standard error.

11

58 **Supplementary Table 8. MR Results for the Relationship Between Hyperopia**  
 59 **and Major Depressive Disorder.**

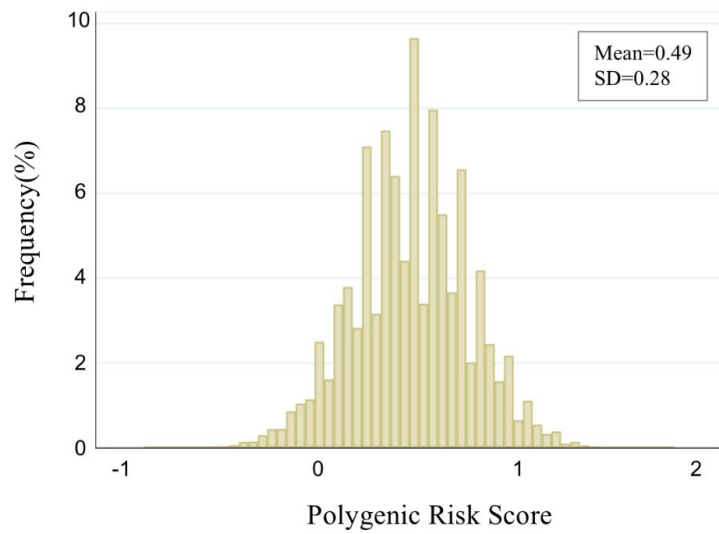
| Exposure  | Outcome                   | Method          | MR analysis        |         | Heterogeneity test |      | Pleiotropy test |         | No. of SNPs |   |
|-----------|---------------------------|-----------------|--------------------|---------|--------------------|------|-----------------|---------|-------------|---|
|           |                           |                 | OR (95% CI)        | P value | Q (df)             | Q_P  | $\beta$ (SE)    | P value |             |   |
| Hyperopia | Major depressive disorder | MR Egger        | 0.87 (-0.38, 0.11) | 0.31    | 4.55 (5)           | 0.47 | -0.00 (0.03)    | 0.72    | 7           |   |
|           |                           | IVW             | 1.00 (-0.06, 0.04) | 0.40    | 5.69 (6)           | 0.46 | 0.02 (0.02)     | 0.34    | 7           |   |
|           |                           | Weighted median | 0.96 (-0.11, 0.04) | 0.30    | -                  | -    | -               | -       | -           | 7 |
|           |                           | Simple model    | 0.96 (-0.15, 0.07) | 0.47    | -                  | -    | -               | -       | -           | 7 |
|           |                           | Weighted model  | 0.96 (-0.14, 0.06) | 0.44    | -                  | -    | -               | -       | -           | 7 |

60 Abbreviations: IVW, inverse variance-weighted; MR, mendelian randomization; SNP,

61 single-nucleotide polymorphism; SE, standard error.

62

12



63

64 **Supplementary Figure 1. Histogram of Polygenic Risk Score of Hyperopia.**<sup>1</sup> The

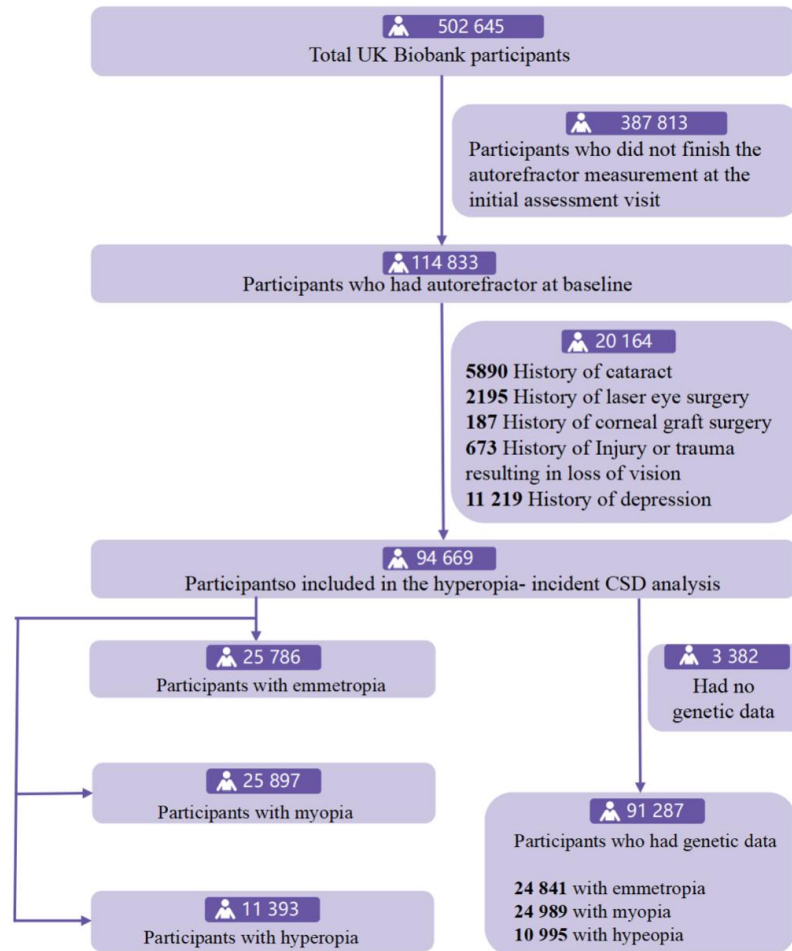
65 calculation of polygenic risk score based on the GWAS study of hyperopia.

66 <sup>1</sup>Tideman JWL, Pärssinen O, Haarman AEG, et al. Evaluation of Shared Genetic Susceptibility to High

67 and Low Myopia and Hyperopia. JAMA ophthalmology. Jun 1 2021;139(6):601-609.

68

13



69

70

**Supplementary Figure 2. Flowchart for population selection for hyperopia from the UK Biobank.**

71

72