Supplementary Methods: Compiling code lists

Coding system	Stroke-specific code list	Broad CVD code list
ICD-9	Previously published codes[1,2]	Previously published codes[1,2]
ICD-10	Previously published codes[1,2]	Previously published codes[1,2]
Read Version 2	Previously published codes[1,2]	Codes compiled for this study[3]
Read Version 3	Codes compiled for this study[3]	Codes compiled for this study[3]
UKB self-reported illness	Codes compiled for this study[3]	Codes compiled for this study[3]

ICD: International Classification of Diseases; UKB: UK Biobank

[1] Woodfield, R., Grant, I., UK Biobank Stroke Outcomes group, UK Biobank Follow-Up and Outcomes Working Group, Sudlow, C. L .M. (2015). Accuracy of Electronic Health Record Data for Identifying Stroke Cases in Large-Scale Epidemiological Studies: A Systematic Review from the UK Biobank Stroke Outcomes Group. PLoS One. 10(10):e0140533.

[2] Rannikmäe, K., Ngoh, K., Bush, K., Al-Shahi Salman, R., Doubal, F., Flaig, R. et al. (2020). Accuracy of identifying incident stroke cases from linked health care data in UK Biobank. Neurology. 95(6):e697-e707.

[3] Process of compiling additional code lists specifically for this study:

- A clinician browsed the Technology Reference Data Update Distribution Service (isd.hscic.gov.uk/trud3/user/guest/group/0/home), the Secure Anonymised Information Linkage databank cerebrovascular diseases dictionary, the Quality Outcomes Framework indicator sets for stroke (www.wales.nhs.uk/), and the CALIBER online data portal (www.caliberresearch.org/) for any relevant codes
- A clinician manually reviewed the entire respective coding systems to identify additional codes
- A clinician used the UK Biobank Resource 592 (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=592) to map codes between ICD-10 and Read Version 2/3 coding systems
- A clinician reviewed the resulting code list and excluded codes that did not seem sensible clinically
- Final code lists were reviewed by expert clinicians (at least two of authors KR, CLMS, ED, RW) and included upon discussion and mutual agreement

Figure S1. Code sources.

1a. Code sources for cases with a stroke-specific code
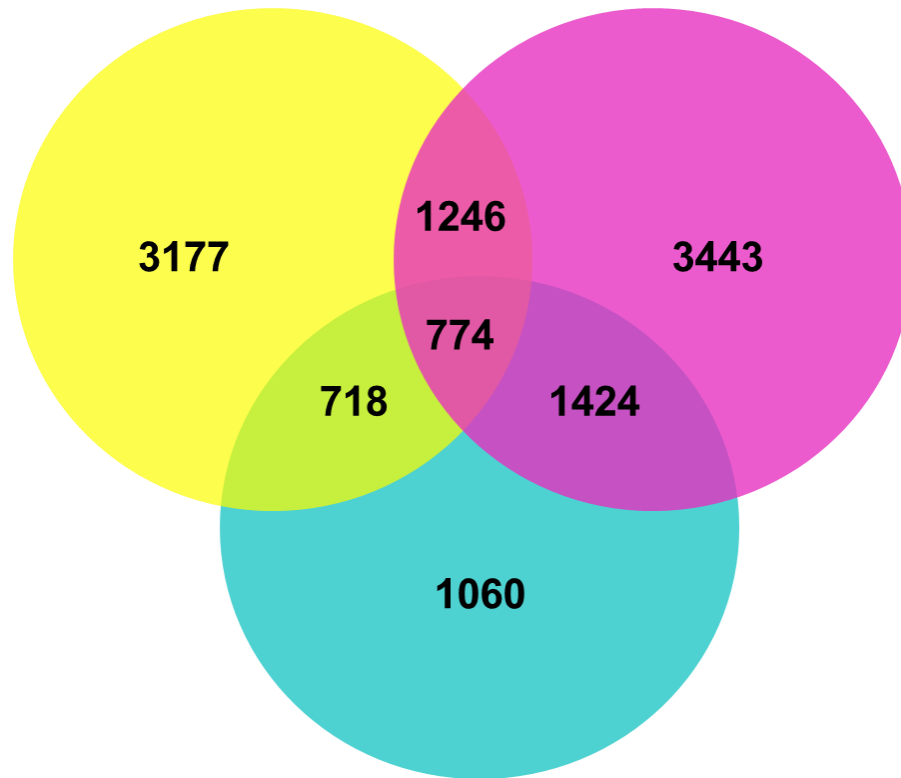
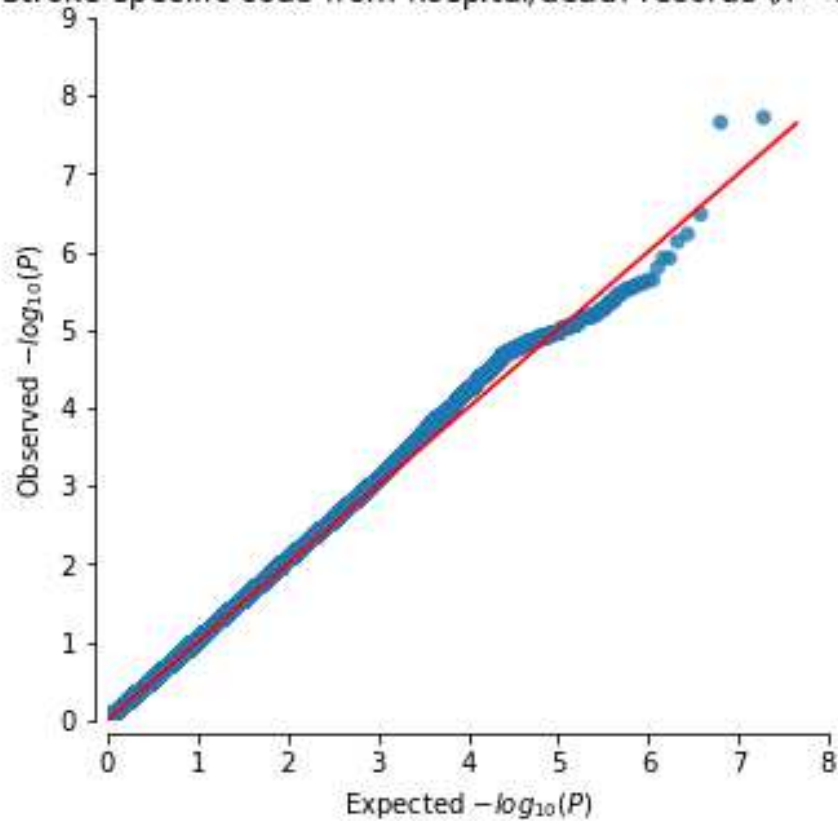2b. Code sources for cases with a broad cerebrovascular disease code

Self-reported event

Code from hospital / death records

Code from primary care

Figure S2. Manhattan and QQ plots for GWAS results for the 12 definitions

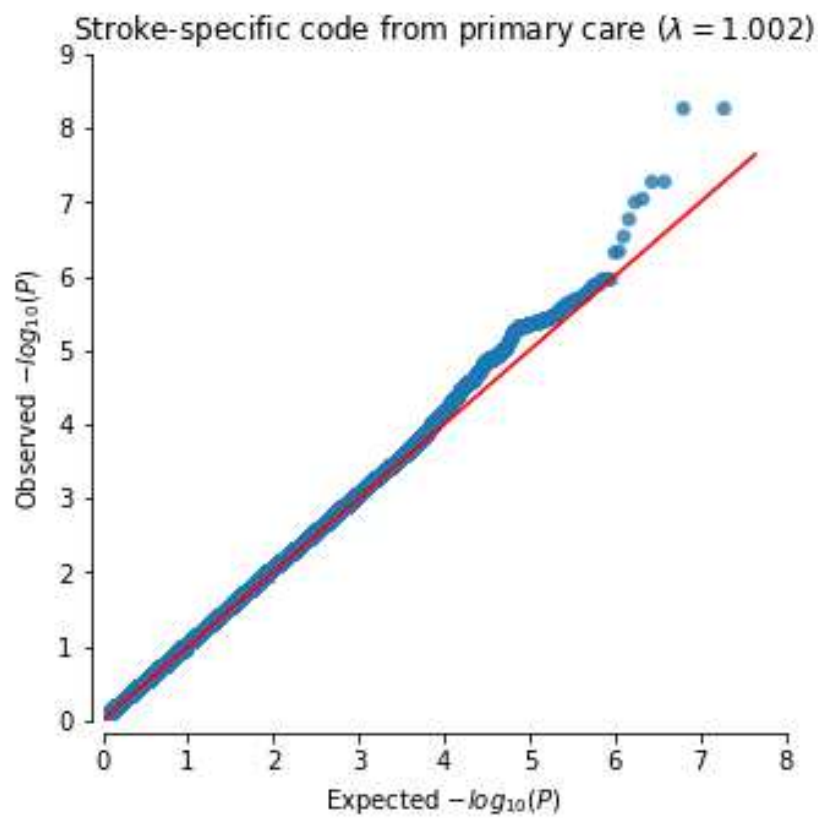**1. Stroke-specific code from hospital/death records**

Stroke-specific code from hospital/death records

Stroke-specific code from hospital/death records ($\lambda = 1.002$)

2. Stroke-specific code from primary care
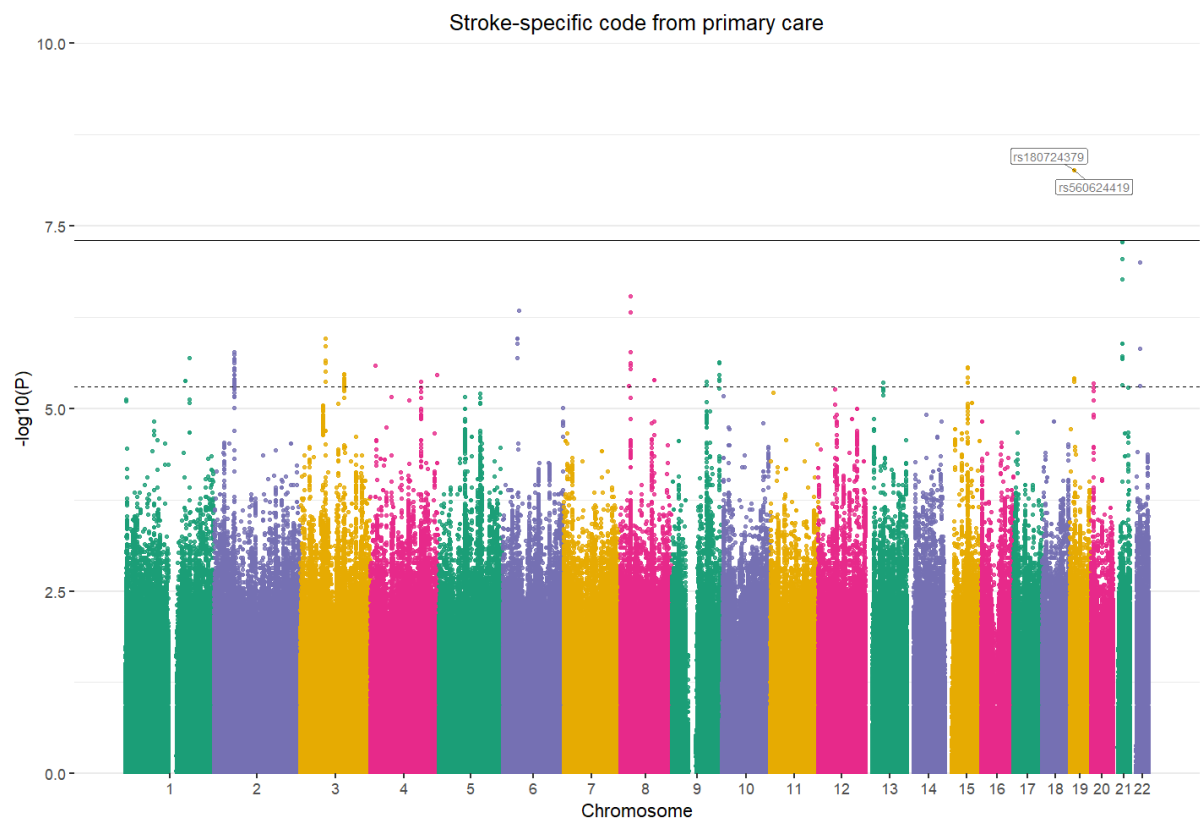
Stroke-specific code from primary care

Stroke-specific code from primary care ($\lambda = 1.002$)

3. Stroke-specific code from any medical setting

Stroke-specific code from any medical setting
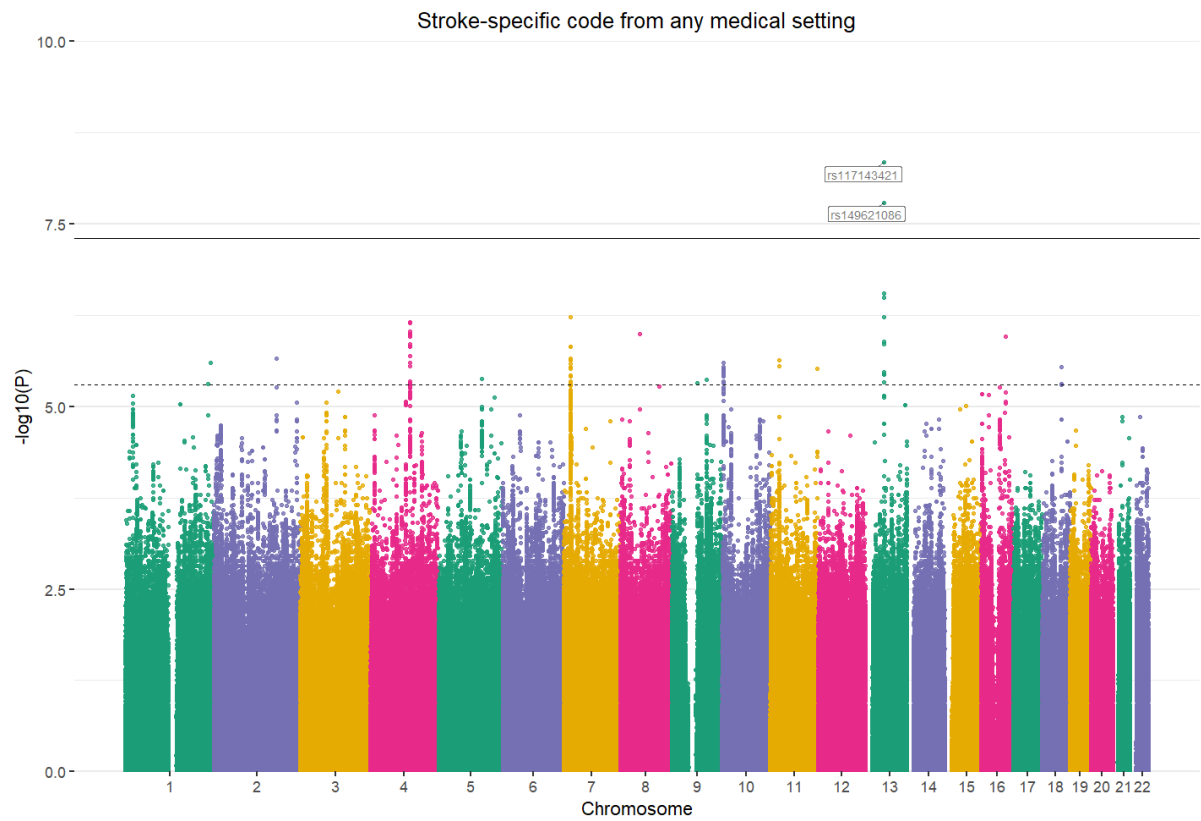
Stroke-specific code from any medical setting ($\lambda = 1.002$)
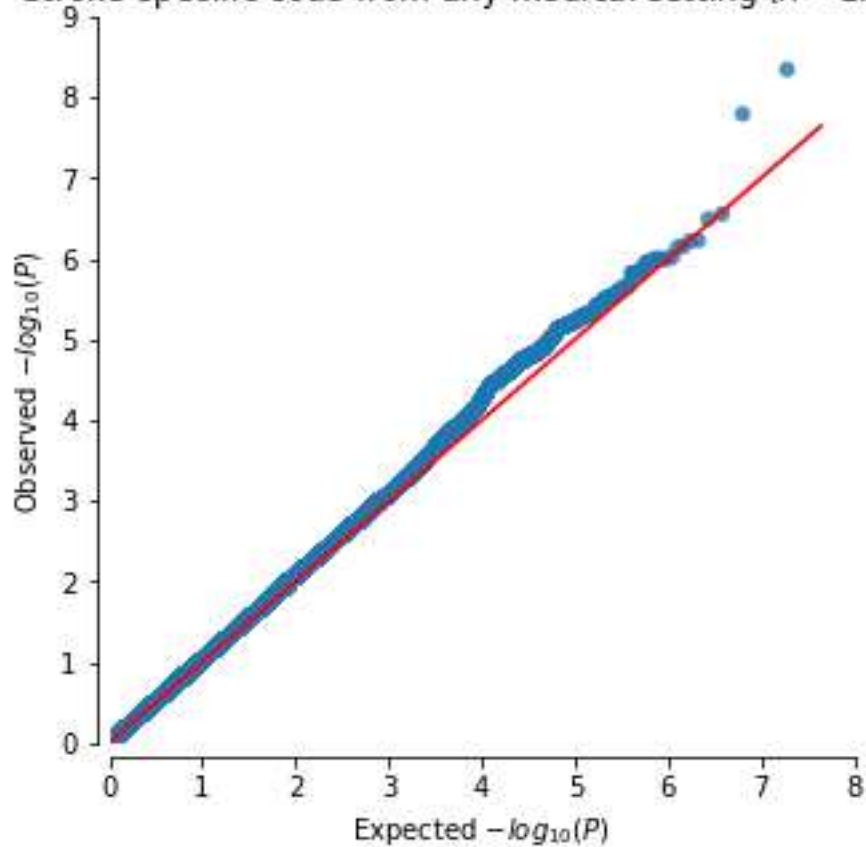
4. Broad CVD code from hospital/death records

Broad CVD code from hospital/death records

rs7256200
rs10414043
rs429358
rs187518102

Broad CVD code from hospital/death records ($\lambda = 1.002$)
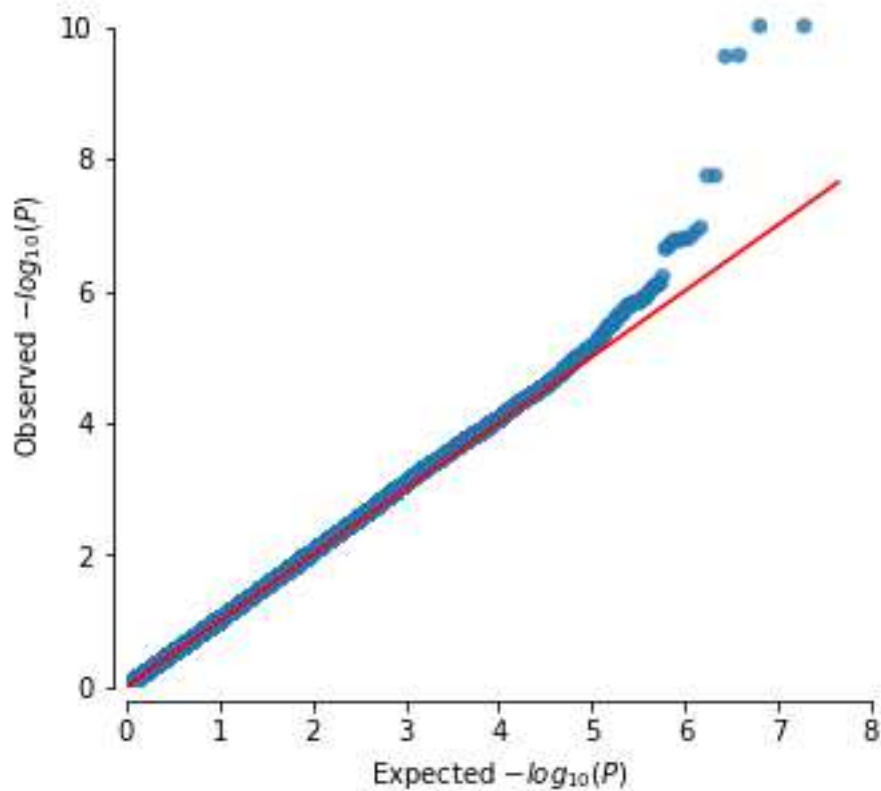
5. Broad CVD code from primary care
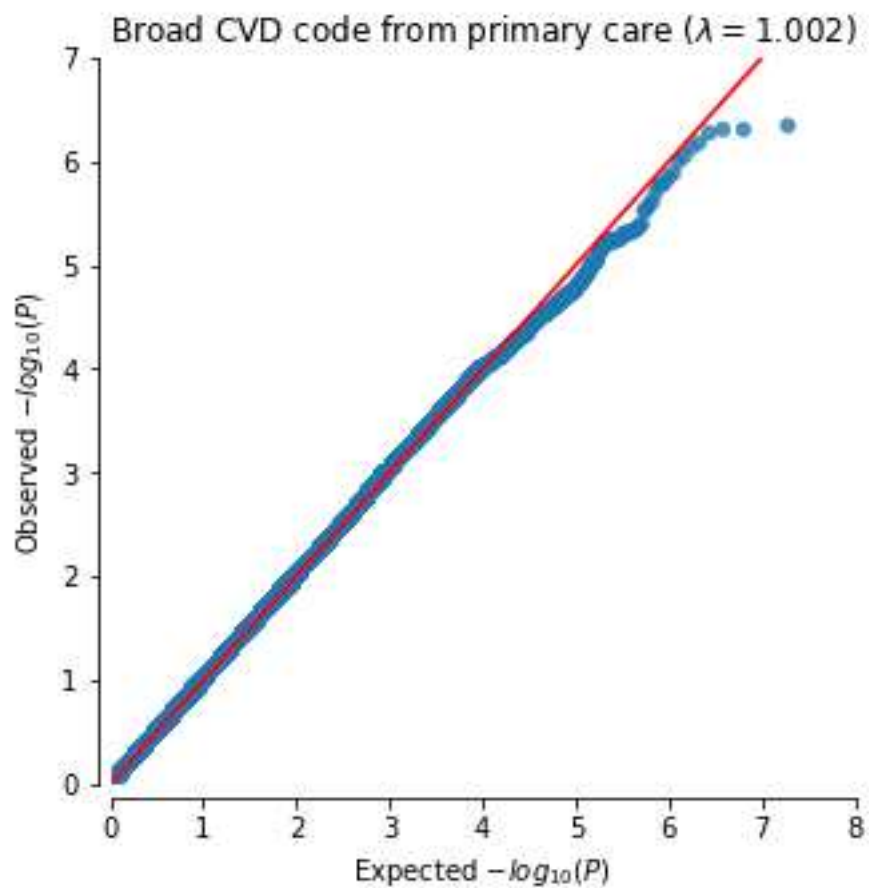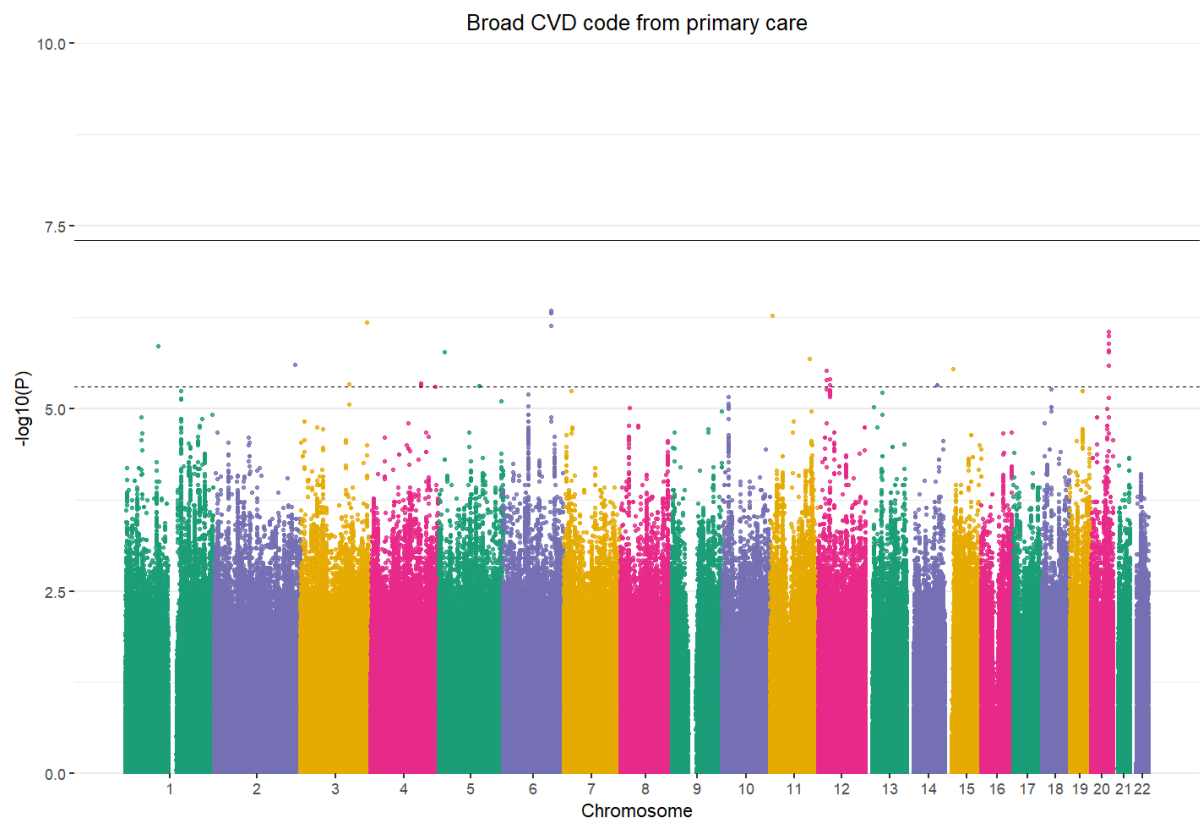
6. Broad CVD code from any medical setting
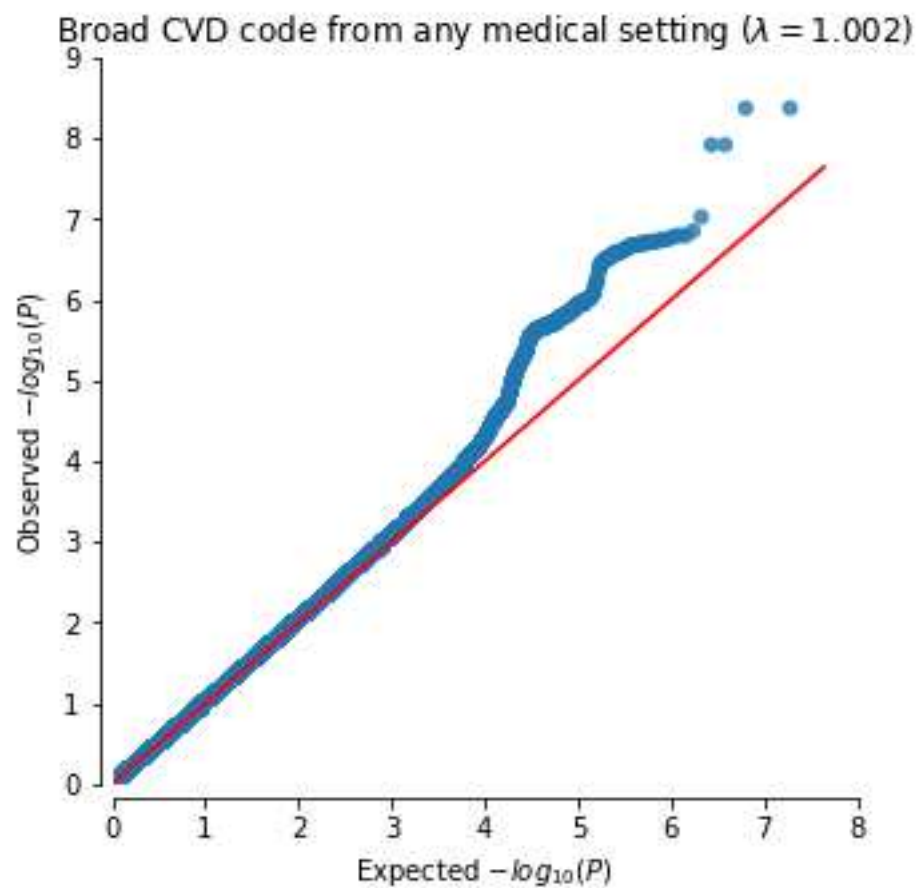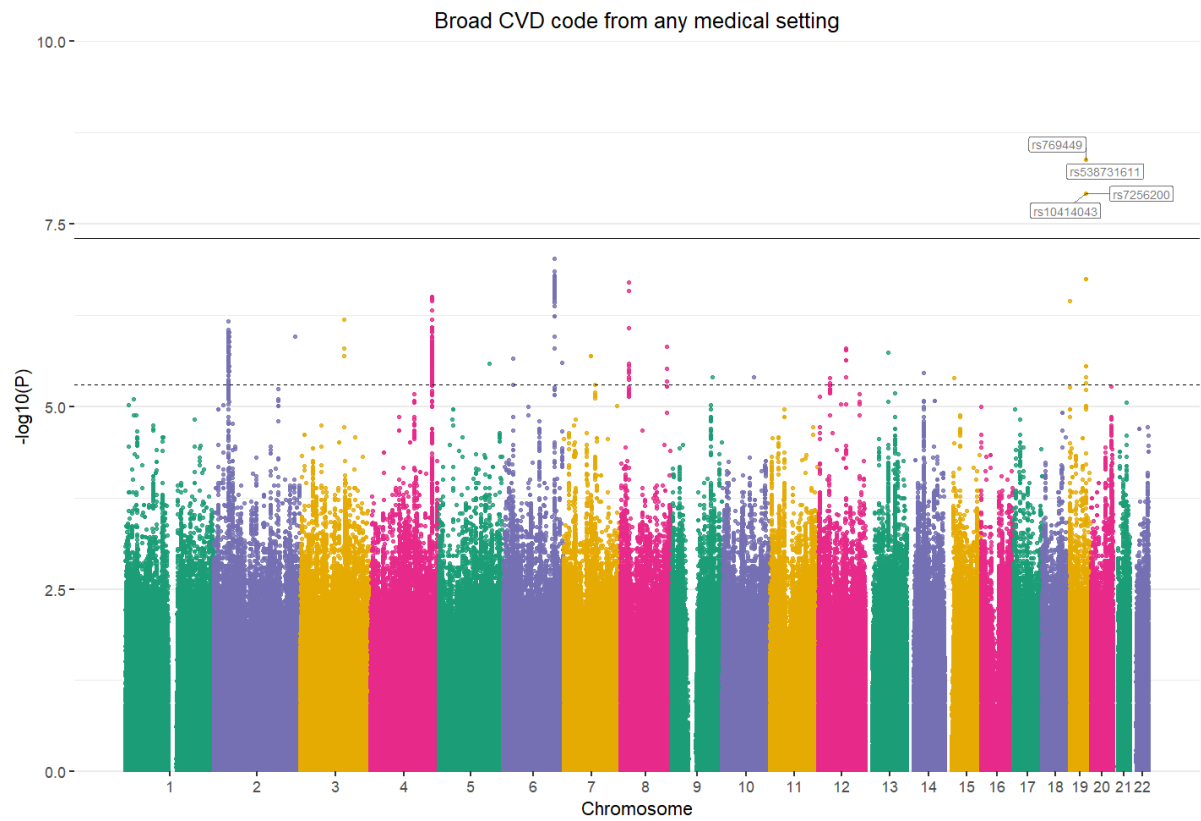
Broad CVD code from any medical setting

rs769449
rs538731611
rs7256200
rs10414043

Broad CVD code from any medical setting ($\lambda = 1.002$)

7. Stroke-specific or broad CVD code from hospital/death records

Stroke-specific or broad CVD code from hospital/death records
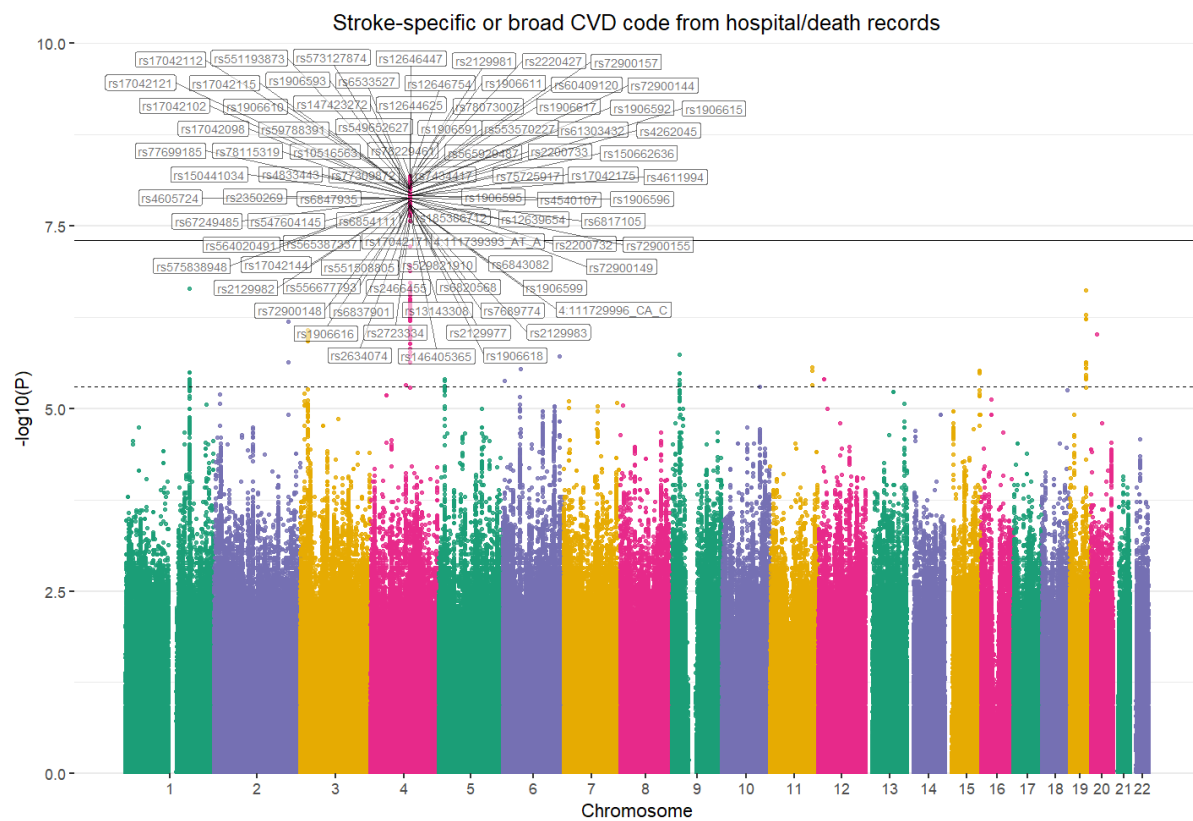
Stroke-specific or broad CVD code from hospital/death records ($\lambda = 1.002$)

8. Stroke-specific or broad CVD code from primary care
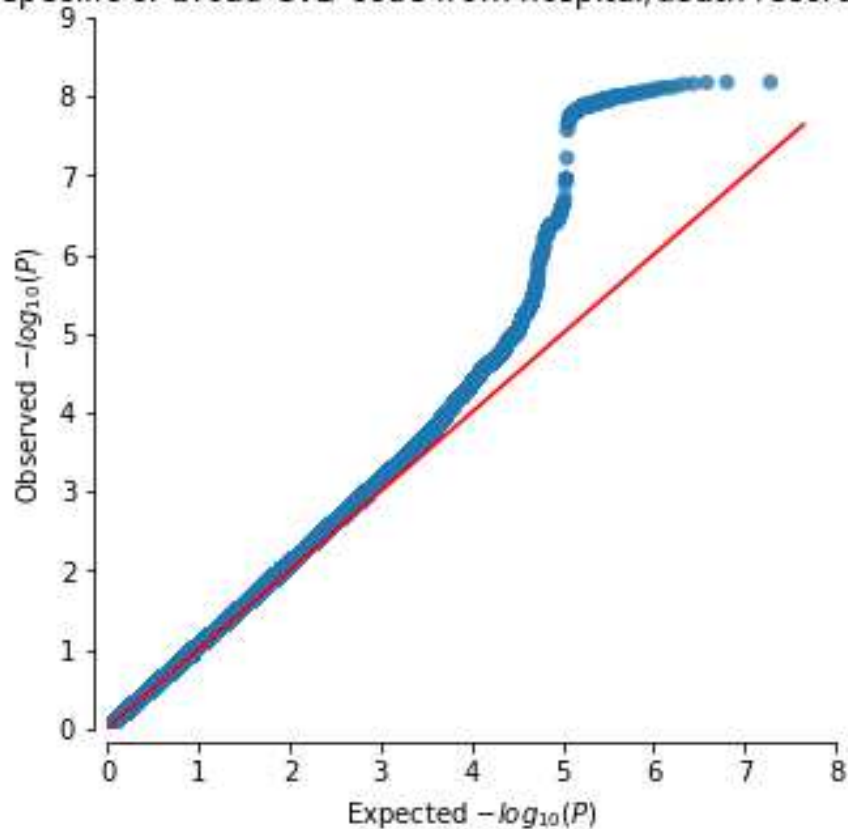
Stroke-specific or broad CVD code from primary care
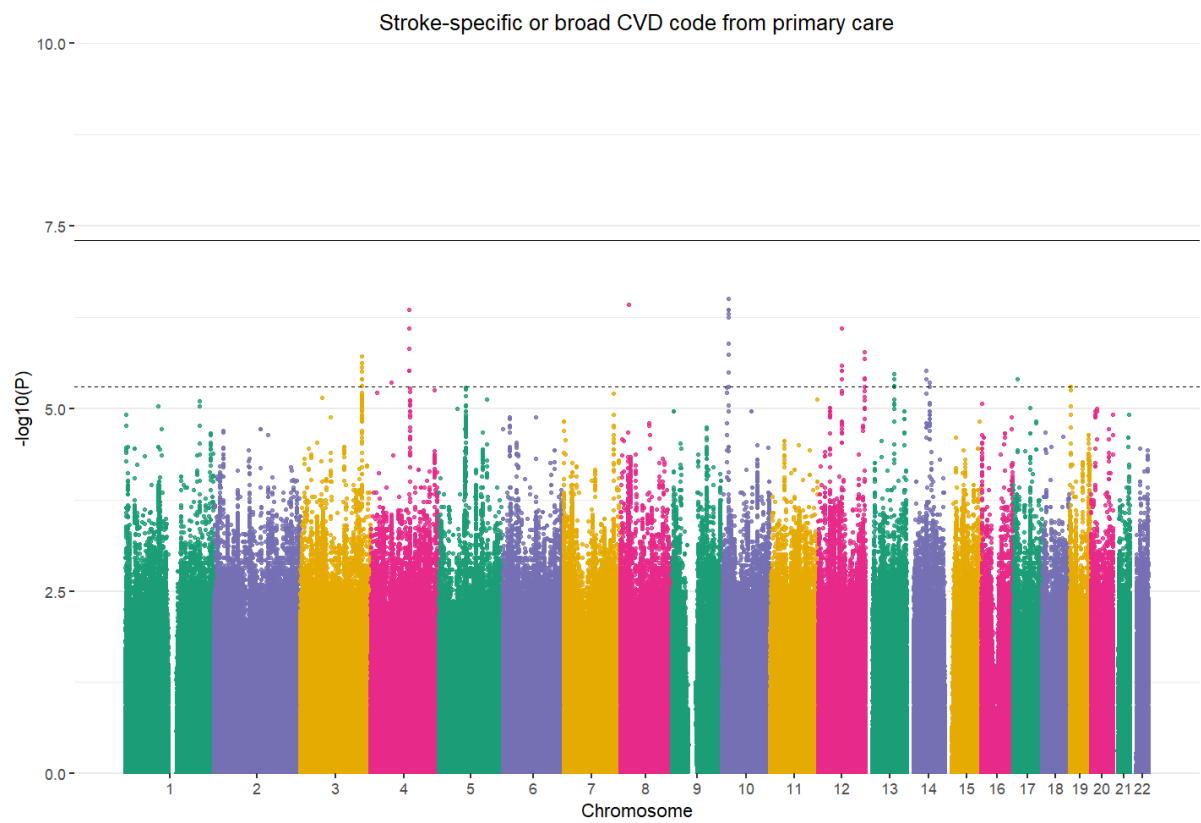
Stroke-specific or broad CVD code from primary care ($\lambda = 1.002$)

9. Stroke-specific or broad CVD code from any medical setting
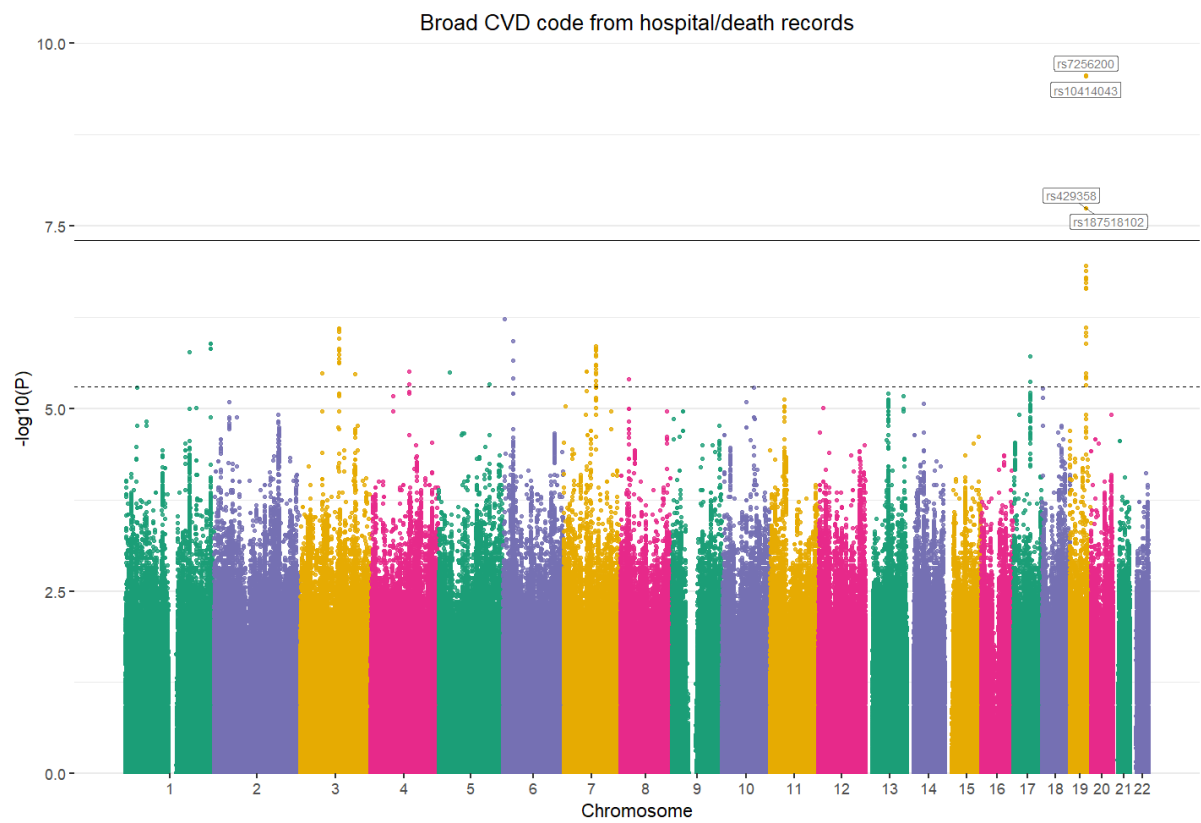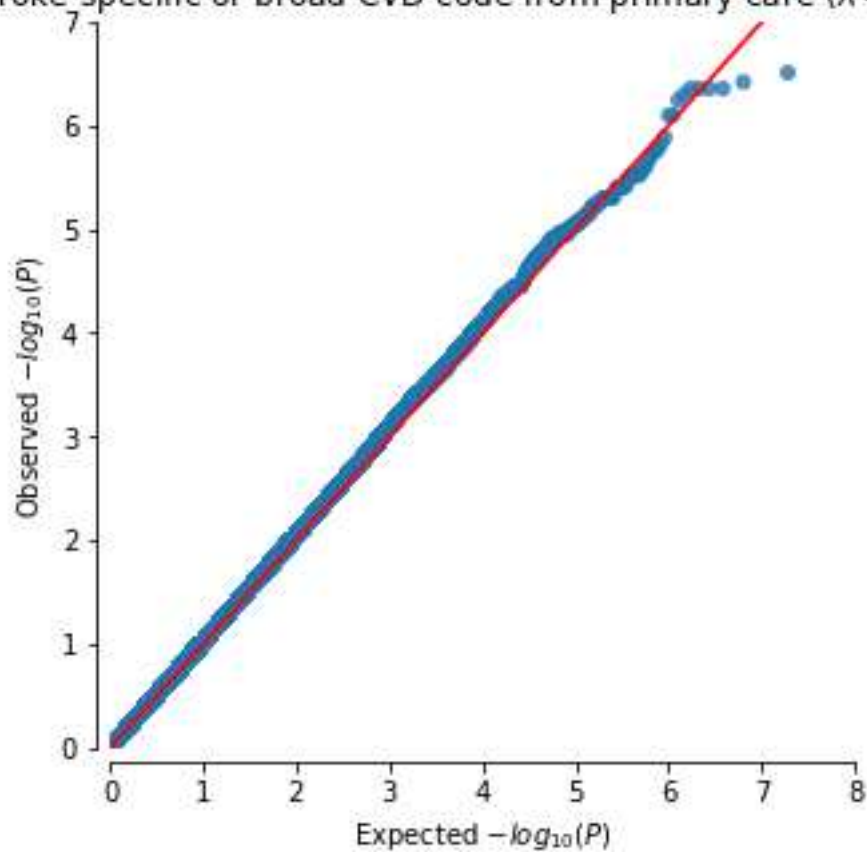

Stroke-specific or broad CVD code from any medical setting

Stroke-specific or broad CVD code from any medical setting ($\lambda = 1.002$)

10. Specific self-reported stroke event
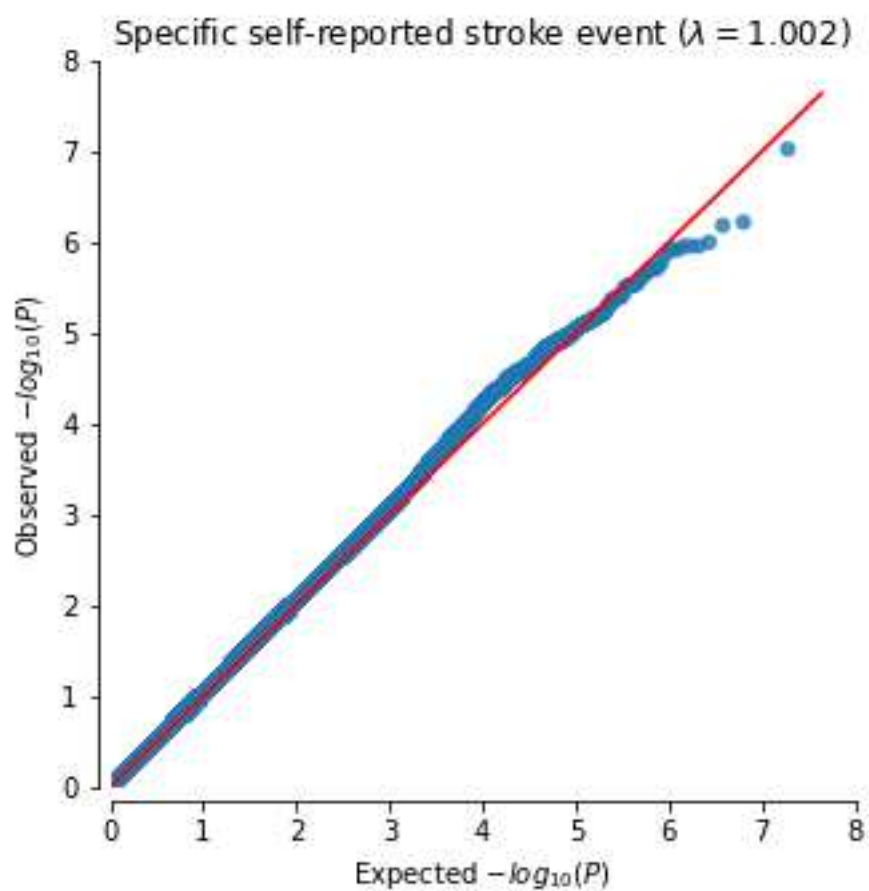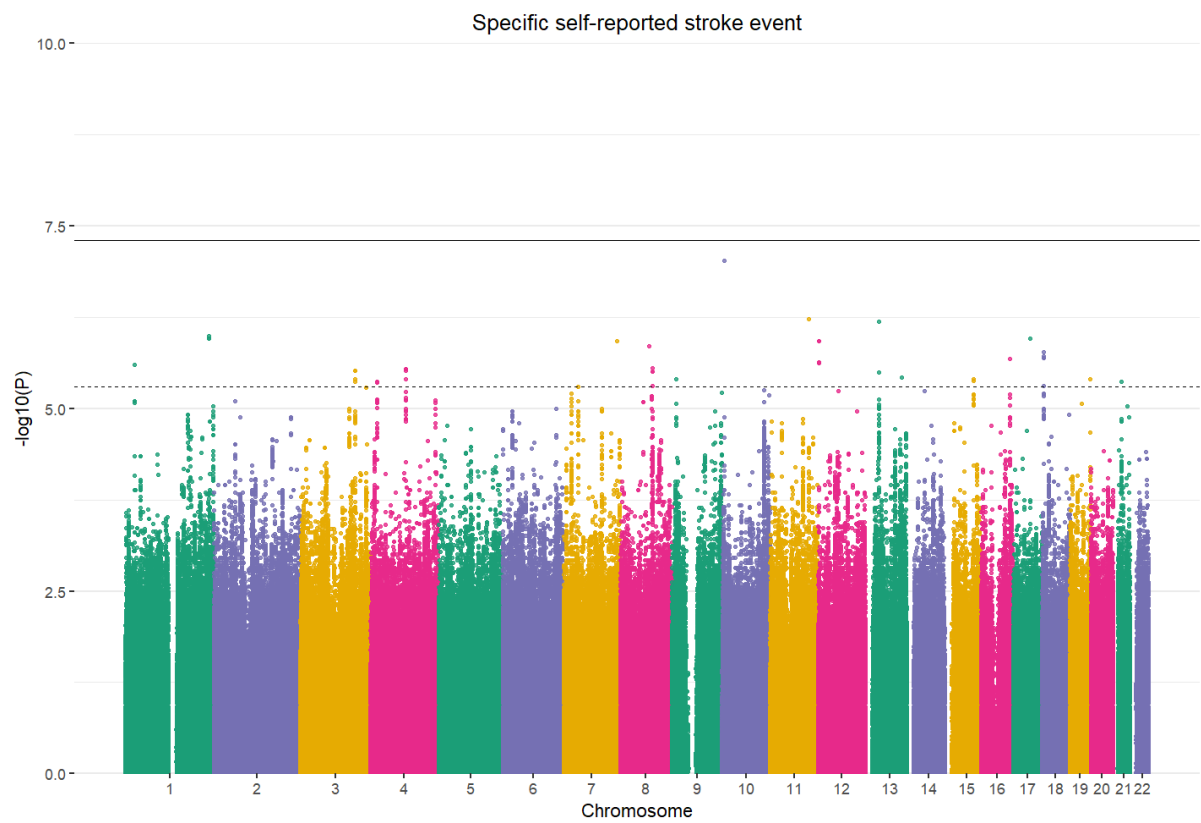
Specific self-reported stroke event

Specific self-reported stroke event ($\lambda = 1.002$)

11. Specific or non-specific self-reported stroke event

Specific or non-specific self-reported stroke event
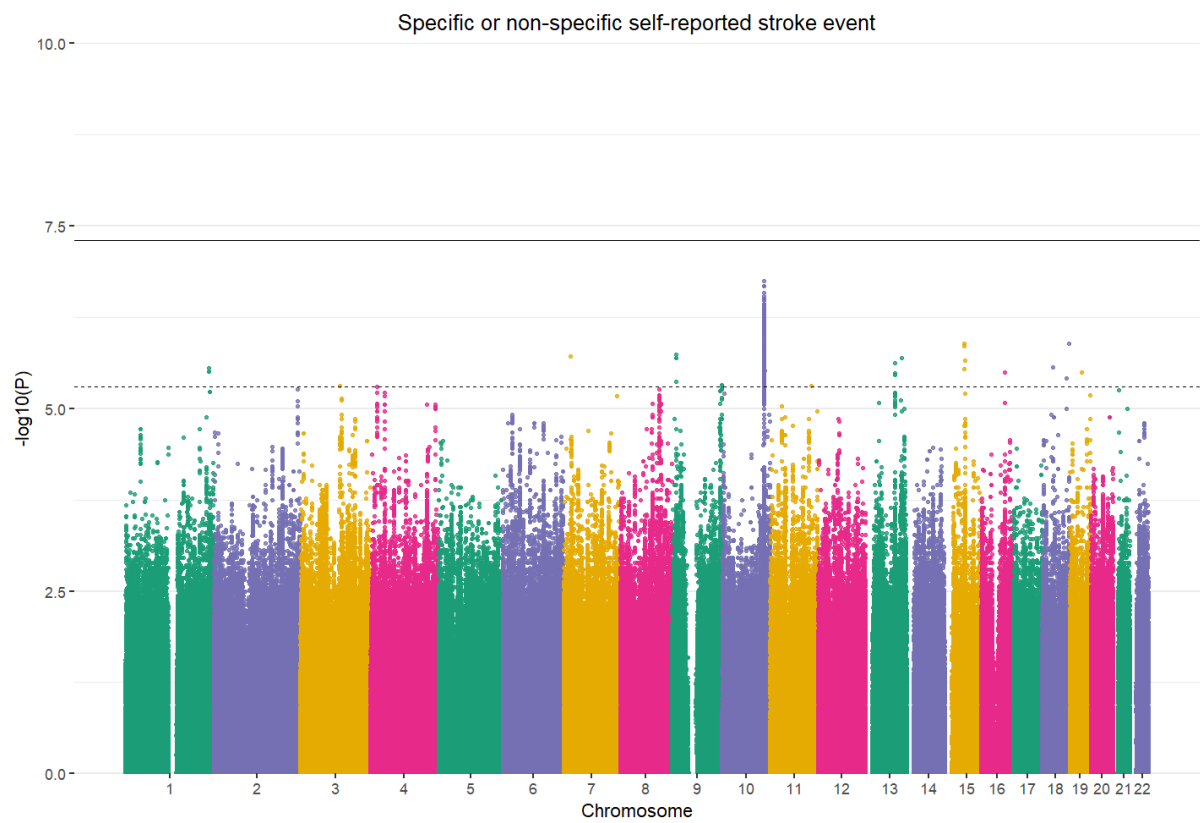
Specific or non-specific self-reported stroke event ($\lambda = 1.002$)

12. Any code or self-reported event

Any code or self-reported event

rs4772887
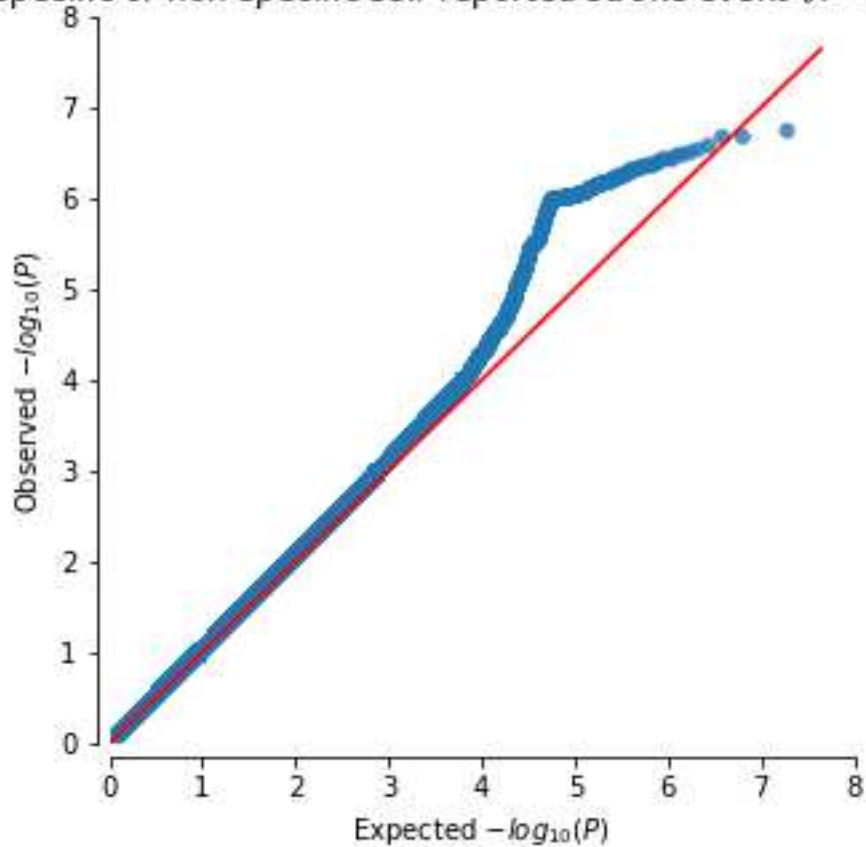
Any code or self-reported event ($\lambda = 1.002$)
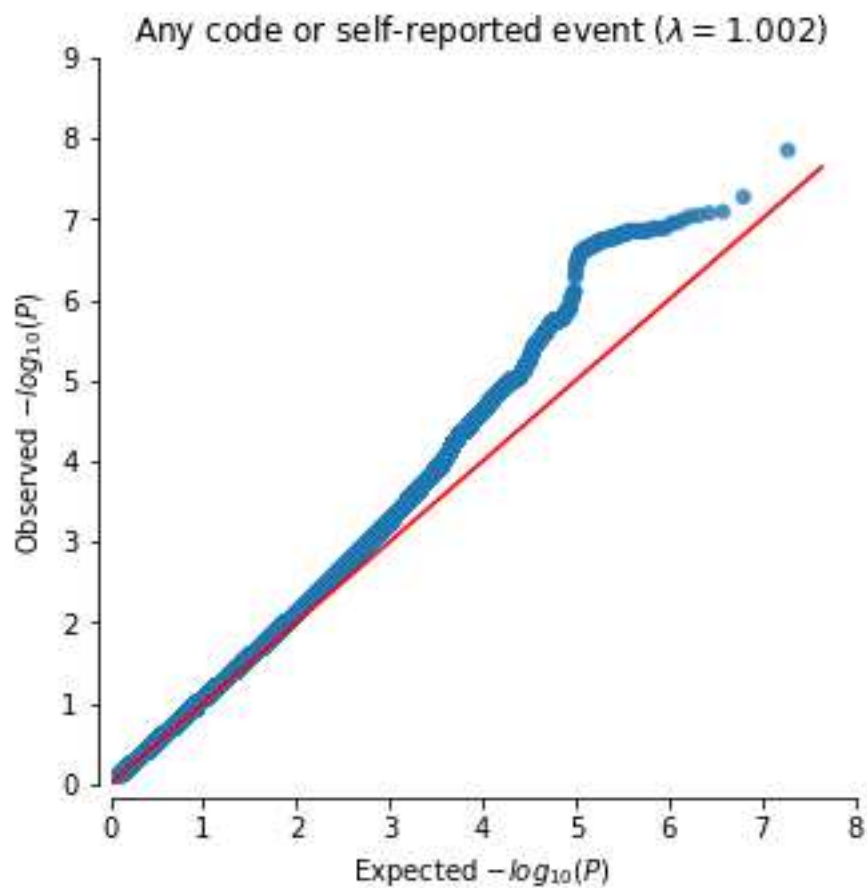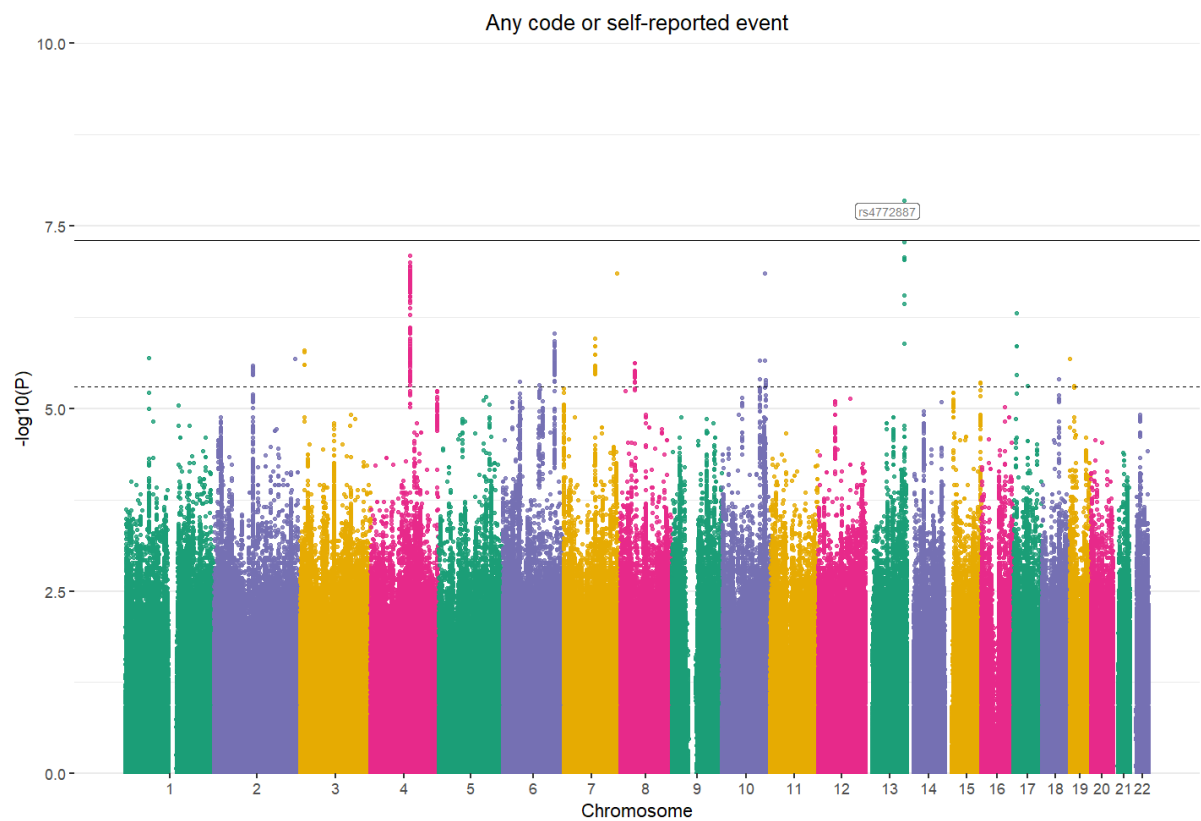
*Dashed line on Manhattan plots indicates a p-value threshold of 0.5×10^{-6} and the solid line a p-value threshold of 0.5×10^{-8}

**λ (lambda): the genomic inflation factor defined as the ratio of the median of the empirically observed distribution of the test statistic to the expected median, thus quantifying the extent of the bulk inflation and the excess false positive rate.

Figure S3. MEGASTROKE stroke-significant loci replicated using UK Biobank stroke definitions

MEGASTROKE odds ratio and p-value is shown for the analyses (European or trans-ethnic) showing the lowest p-value.

2a.

CHR9: rs635634 C=>T (ABO)

	OR (95% CI)	P-value
Megastroke	1.08 (1.05-1.11)	9.18x10-9*
Stroke-specific code from hospital/death records	1.07 (1.03-1.12)	0.0016
Stroke-specific code from primary care	1.08 (1.02-1.14)	0.0089
Stroke-specific code from any medical setting	1.08 (1.03-1.12)	0.00018*
Broad CVD code from hospital/death records	1.02 (0.97-1.07)	0.47
Broad CVD code from primary care	1 (0.94-1.06)	0.99
Broad CVD code from any medical setting	1 (0.96-1.04)	0.86
Stroke-specific or broad CVD code from hospital/death records	1.05 (1.01-1.08)	0.0044
Stroke-specific or broad CVD code from primary care	1.04 (1-1.08)	0.063
Stroke-specific or Broad CVD code from any medical setting	1.04 (1.01-1.07)	0.0043
Specific self-reported stroke event	1.09 (1.04-1.15)	9.8x10-5*
Specific or non-specific self-reported stroke event	1.1 (1.05-1.14)	5.8x10-6*
Any code or self-reported event	1.05 (1.02-1.07)	0.00043*

OR (95% CI): 0.9 1 1.1 1.2 1.3 1.4

2b.

CHR10: rs2295786 T=>A (SH3PXD2A)

	OR (95% CI)	P-value
Megastroke	**1.05 (1.04-1.07)**	**1.86x10-10***
Stroke-specific code from hospital/death records	1.08 (1.04-1.11)	6.1x10-5*
Stroke-specific code from primary care	1.06 (1.01-1.11)	0.014
Stroke-specific code from any medical setting	**1.07 (1.04-1.11)**	**1.5x10-5***
Broad CVD code from hospital/death records	1.04 (1-1.08)	0.062
Broad CVD code from primary care	0.99 (0.94-1.04)	0.63
Broad CVD code from any medical setting	**1.01 (0.98-1.04)**	**0.59**
Stroke-specific or broad CVD code from hospital/death records	1.06 (1.03-1.09)	1.9x10-5*
Stroke-specific or broad CVD code from primary care	1.02 (0.99-1.06)	0.16
Stroke-specific or Broad CVD code from any medical setting	**1.04 (1.02-1.07)**	**4.0x10-4***
Specific self-reported stroke event	1.05 (1.01-1.09)	0.0096
Specific or non-specific self-reported stroke event	**1.04 (1.01-1.08)**	**0.021**
Any code or self-reported event	**1.05 (1.03-1.07)**	**5.1x10-6***

OR (95% CI)
0.9 1 1.1 1.2 1.3 1.4

2c.

CHR12: rs3184504 C=>T (SH2B3)

	OR (95% CI)	P-value
Megastroke	**1.08 (1.06-1.1)**	**2.17x10-14***
Stroke-specific code from hospital/death records	1.05 (1.01-1.08)	0.007
Stroke-specific code from primary care	1.04 (1-1.09)	0.067
Stroke-specific code from any medical setting	**1.04 (1.01-1.07)**	**0.0096**
Broad CVD code from hospital/death records	1.01 (0.97-1.04)	0.76
Broad CVD code from primary care	1.01 (0.97-1.06)	0.52
Broad CVD code from any medical setting	**1 (0.97-1.03)**	**0.83**
Stroke-specific or broad CVD code from hospital/death records	1.03 (1-1.05)	0.026
Stroke-specific or broad CVD code from primary care	1.03 (1-1.06)	0.077
Stroke-specific or Broad CVD code from any medical setting	**1.02 (1-1.05)**	**0.04**
Specific self-reported stroke event	1.07 (1.03-1.11)	0.00047*
Specific or non-specific self-reported stroke event	**1.06 (1.03-1.1)**	**0.00019***
Any code or self-reported event	**1.03 (1.01-1.05)**	**0.0068**

0.9   1   1.1   1.2   1.3   1.4
OR (95% CI)

2d.

CHR9: rs7859727 C=>T (Chr9p21)

		OR (95% CI)	P-value
Megastroke		**1.05 (1.03-1.07)**	**4.22x10-10***
Stroke-specific code from hospital/death records		1.07 (1.04-1.11)	2.7x10-5*
Stroke-specific code from primary care		1.06 (1.01-1.11)	0.0091
Stroke-specific code from any medical setting		**1.06 (1.03-1.09)**	**8.1x10-5***
Broad CVD code from hospital/death records		1.04 (1-1.08)	0.032
Broad CVD code from primary care		1.04 (0.99-1.08)	0.11
Broad CVD code from any medical setting		**1.04 (1.01-1.07)**	**0.018**
Stroke-specific or broad CVD code from hospital/death records		1.06 (1.03-1.09)	4.5x10-6*
Stroke-specific or broad CVD code from primary care		1.05 (1.02-1.08)	0.0027
Stroke-specific or Broad CVD code from any medical setting		**1.05 (1.03-1.07)**	**5.3x10-6***
Specific self-reported stroke event		1.01 (0.97-1.05)	0.62
Specific or non-specific self-reported stroke event		**1.02 (0.98-1.05)**	**0.32**
Any code or self-reported event		**1.04 (1.02-1.06)**	**6.3x10-5***

0.9 1 1.1 1.2 1.3 1.4
OR (95% CI)

Appendix 1

MEGASTROKE CONSORTIUM

Rainer Malik [1], Ganesh Chauhan [2], Matthew Traylor [3], Muralidharan Sargurupremraj [4,5], Yukinori Okada [6,7,8], Aniket Mishra [4,5], Loes Rutten-Jacobs [3], Anne-Katrin Giese [9], Sander W van der Laan [10], Solveig Gretarsdottir [11], Christopher D Anderson [12,13,14,14], Michael Chong [15], Hieab HH Adams [16,17], Tetsuro Ago [18], Peter Almgren [19], Philippe Amouyel [20,21], Hakan Ay [22,13], Traci M Bartz [23], Oscar R Benavente [24], Steve Bevan [25], Giorgio B Boncoraglio [26], Robert D Brown, Jr. [27], Adam S Butterworth [28,29], Caty Carrera [30,31], Cara L Carty [32,33], Daniel I Chasman [34,35], Wei-Min Chen [36], John W Cole [37], Adolfo Correa [38], Ioana Cotlarciuc [39], Carlos Cruchaga [40,41], John Danesh [28,42,43,44], Paul IW de Bakker [45,46], Anita L DeStefano [47,48], Marcel den Hoed [49], Qing Duan [50], Stefan T Engelter [51,52], Guido J Falcone [53,54], Rebecca F Gottesman [55], Raji P Grewal [56], Vilmundur Gudnason [57,58], Stefan Gustafsson [59], Jeffrey Haessler [60], Tamara B Harris [61], Ahamad Hassan [62], Aki S Havulinna [63,64], Susan R Heckbert [65], Elizabeth G Holliday [66,67], George Howard [68], Fang-Chi Hsu [69], Hyacinth I Hyacinth [70], M Arfan Ikram [16], Erik Ingelsson [71,72], Marguerite R Irvin [73], Xueqiu Jian [74], Jordi Jiménez-Conde [75], Julie A Johnson [76,77], J Wouter Jukema [78], Masahiro Kanai [6,7,79], Keith L Keene [80,81], Brett M Kissela [82], Dawn O Kleindorfer [82], Charles Kooperberg [60], Michiaki Kubo [83], Leslie A Lange [84], Carl D Langefeld [85], Claudia Langenberg [86], Lenore J Launer [87], Jin-Moo Lee [88], Robin Lemmens [89,90], Didier Leys [91], Cathryn M Lewis [92,93], Wei-Yu Lin [28,94], Arne G Lindgren [95,96], Erik Lorentzen [97], Patrik K Magnusson [98], Jane Maguire [99], Ani Manichaikul [36], Patrick F McArdle [100], James F Meschia [101], Braxton D Mitchell [100,102], Thomas H Mosley [103,104], Michael A Nalls [105,106], Toshiharu Ninomiya [107], Martin J O'Donnell [15,108], Bruce M Psaty [109,110,111,112], Sara L Pulit [113,45], Kristiina Rannikmäe [114,115], Alexander P Reiner [65,116], Kathryn M Rexrode [117], Kenneth Rice [118], Stephen S Rich [36], Paul M Ridker [34,35], Natalia S Rost [9,13], Peter M Rothwell [119], Jerome I Rotter [120,121], Tatjana Rundek [122], Ralph L Sacco [122], Saori Sakaue [7,123], Michele M Sale [124], Veikko Salomaa [63], Bishwa R Sapkota [125], Reinhold Schmidt [126], Carsten O Schmidt [127], Ulf Schminke [128], Pankaj Sharma [39], Agnieszka Slowik [129], Cathie LM Sudlow [114,115], Christian Tanislav [130], Turgut Tatlisumak [131,132], Kent D Taylor [120,121], Vincent NS Thijs [133,134], Gudmar Thorleifsson [11], Unnur Thorsteinsdottir [11], Steffen Tiedt [1], Stella Trompet [135], Christophe Tzourio [5,136,137], Cornelia M van Duijn [138,139], Matthew Walters [140], Nicholas J Wareham [86], Sylvia Wassertheil-Smoller [141], James G Wilson [142], Kerri L Wiggins [109], Qiong Yang [47], Salim Yusuf [15], Najaf Amin [16], Hugo S Aparicio [185,48], Donna K Arnett [186], John Attia [187], Alexa S Beiser [47,48], Claudine Berr [188], Julie E Buring [34,35], Mariana Bustamante [189], Valeria Caso [190], Yu-Ching Cheng [191], Seung Hoan Choi [192,48], Ayesha Chowhan [185,48], Natalia Cullell [31], Jean-François Dartigues [193,194], Hossein Delavaran [95,96], Pilar Delgado [195], Marcus Dörr [196,197], Gunnar Engström [19], Ian Ford [198], Wander S Gurpreet [199], Anders Hamsten [200,201], Laura Heitsch [202], Atsushi Hozawa [203], Laura Ibanez [204], Andreea Ilinca [95,96], Martin Ingelsson [205], Motoki Iwasaki [206], Rebecca D Jackson [207], Katarina Jood [208], Pekka Jousilahti [63], Sara Kaffashian [4,5], Lalit Kalra [209], Masahiro Kamouchi [210], Takanari Kitazono [211], Olafur Kjartansson [212], Manja Kloss [213], Peter J Koudstaal [214], Jerzy Krupinski [215], Daniel L Labovitz [216], Cathy C Laurie [118], Christopher R Levi [217], Linxin Li [218], Lars Lind [219], Cecilia M Lindgren [220,221],

Vasileios Lioutas [222,48], Yong Mei Liu [223], Oscar L Lopez [224], Hirata Makoto [225], Nicolas Martinez-Majander [172], Koichi Matsuda [225], Naoko Minegishi [203], Joan Montaner [226], Andrew P Morris [227,228], Elena Muiño [31], Martina Müller-Nurasyid [229,230,231], Bo Norrving [95,96], Soichi Ogishima [203], Eugenio A Parati [232], Leema Reddy Peddareddygari [56], Nancy L Pedersen [98,233], Joanna Pera [129], Markus Perola [63,234], Alessandro Pezzini [235], Silvana Pileggi [236], Raquel Rabionet [237], Iolanda Riba-Llena [30], Marta Ribasés [238], Jose R Romero [185,48], Jaume Roquer [239,240], Anthony G Rudd [241,242], Antti-Pekka Sarin [243,244], Ralhan Sarju [199], Chloe Sarnowski [47,48], Makoto Sasaki [245], Claudia L Satizabal [185,48], Mamoru Satoh [245], Naveed Sattar [246], Norie Sawada [206], Gerli Sibolt [172], Ásgeir Sigurdsson [247], Albert Smith [248], Kenji Sobue [245], Carolina Soriano-Tárraga [240], Tara Stanne [249], O Colin Stine [250], David J Stott [251], Konstantin Strauch [229,252], Takako Takai [203], Hideo Tanaka [253,254], Kozo Tanno [245], Alexander Teumer [255], Liisa Tomppo [172], Nuria P Torres-Aguila [31], Emmanuel Touze [256,257], Shoichiro Tsugane [206], Andre G Uitterlinden [258], Einar M Valdimarsson [259], Sven J van der Lee [16], Henry Völzke [255], Kenji Wakai [253], David Weir [260], Stephen R Williams [261], Charles DA Wolfe [241,242], Quenna Wong [118], Huichun Xu [191], Taiki Yamaji [206], Dharambir K Sanghera [125,169,170], Olle Melander [19], Christina Jern [171], Daniel Strbian [172,173], Israel Fernandez-Cadenas [31,30], W T Longstreth, Jr [174,65], Arndt Rolfs [175], Jun Hata [107], Daniel Woo [82], Jonathan Rosand [12,13,14], Guillaume Pare [15], Jemma C Hopewell [176], Danish Saleheen [177], Kari Stefansson [11,178], Bradford B Worrall [179], Steven J Kittner [37], Sudha Seshadri [180,48], Myriam Fornage [74,181], Hugh S Markus [3], Joanna MM Howson [28], Yoichiro Kamatani [6,182], Stephanie Debette [4,5], Martin Dichgans [1,183,184]

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33 Center for Translational Science, George Washington University, Washington, DC, USA
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