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1 "Making stillbirths visible: A systematic review of globally reported causes of stillbirth"

2 **Short title:** Global reporting of causes of stillbirth

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56 Abstract

57 Background

- 58 Stillbirth is a global health problem. The World Health Organization (WHO) application of the
- 59 International Classification of Diseases for perinatal mortality (ICD-PM) aims to improve data on
- 60 stillbirth to enable prevention.
- 61 *Objectives*
- To identify globally reported causes of stillbirth, classification systems, and alignment with the ICD-PM.
- 64 Search strategy
- 65 We searched CINAHL, EMBASE, Medline, Global Health and Pubmed from 2009-2016.
- 66 Selection criteria
- 67 Reports of stillbirth causes in unselective cohorts.
- 68 Data collection and analysis
- 69 Pooled estimates of causes were derived for country representative reports. Systems and causes were
- assessed for alignment with the ICD-PM. Data are presented by income setting (low, middle and high
- 71 income; LIC, MIC, HIC).
- 72 Main results
- 73 85 reports from 50 countries (489,089 stillbirths) were included. The most frequent categories were
- 74 Unexplained, Antepartum haemorrhage and Other (all settings), Infection and Hypoxic peripartum
- 75 (LIC), and *Placental* (MIC, HIC). Overall report quality was low. Only one classification system
- fully aligned with ICD-PM. All stillbirth causes mapped to ICD-PM. In a subset from HIC mapping
- 77 obscured major causes.
- 78 Conclusion
- 79 There is a paucity of quality information on causes of stillbirth globally. Improving investigation of
- 80 stillbirths and standardisation of audit and classification is urgently needed and should be achievable

- 81 in all well-resourced settings. Implementation of the WHO Perinatal Mortality Audit and Review
- 82 guide particularly across high burden settings is needed.
- 83 Funding
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- 86 Keywords
- 87 Stillbirth, classification, systems, cause of death, ICD
- 88 *Tweetable Abstract*
- 89 Urgent need to improve data on causes of stillbirths across all settings to meet global targets.

90

91 Introduction

The global stillbirth rate (≥ 28 completed weeks' gestation) is estimated to be 18.4 per 1000 births¹ or 92 around 2.6 million stillbirths each year¹. The World Health Organization's (WHO's) Every Newborn 93 94 Action Plan aims to reduce the stillbirth rate to 12 or fewer per 1000 births by 2030 in every country, 95 and for countries already meeting this target to reduce equity gaps². However, with an estimated annual reduction rate of 2.0% between 2000 and 2015¹, half that for neonatal deaths, progress has 96 97 been slow. Identifying interventions to achieve such a target would be facilitated by cross-country 98 and inter-country comparisons of the causes of stillbirth. Moreover, while national neonatal causes of death are regularly published through the United Nations^{1,3}, there is currently no systematic global 99 100 reporting of causes of stillbirth. The WHO recommends use of the International Statistical 101 Classification of Diseases and Health Related Problems (ICD) for classification of perinatal deaths 102 for international reporting⁴. However, limitations in ICD for classifying stillbirths⁵ has resulted in numerous disparate systems currently in use⁶, thus limiting global comparisons. In 2016, WHO 103 104 released ICD Perinatal Mortality (ICD-PM) as part of the WHO Perinatal Mortality Audit and Review guide⁷. The ICD-PM is an application of ICD and holds promise as an important step in improving 105 106 global and local reporting of causes of stillbirths and neonatal deaths⁸. The ICD-PM aims to collect, 107 at a minimum, timing of death and clinically defined causes and associated conditions.

108 **Objectives**

Following on the introduction of the ICD-PM, we aimed to identify globally reported causes of stillbirth in order to support progress toward the WHO Every Newborn Action Plan stillbirth rate target. The specific objectives were to:

- Describe the current status of global reporting of stillbirth causes, including reported causes
 and classification systems used;
- 2. Pool results from country representative reports to identify commonly reported causes of
 stillbirth, stratified by income setting (high-, middle-, and low-income); and

3. Assess alignment of systems used and reported causes of stillbirths with the ICD-PM forcountry representative reports.

118 Methods

This systematic review was conducted and reported according to the PRISMA checklist⁹. The protocol has not been published. Two authors independently undertook screening of reports, selection, data extraction and quality assessment.

122 Eligibility criteria

All published and unpublished cohort and cross-sectional reports from 1 January 2009 to 31 December 2016 which presented causes of stillbirth were eligible. Reports were excluded if they: included non-consecutive or selected subgroups, e.g. preterm; aimed only to identify risk factors or did not provide data on causes in an extractable format (for complete study selection see Figure S1).

127 Information sources

We searched PubMed, Global Health, Cinahl, Medline and Embase without language restrictions.
We identified national reports through web-based systematic searches (Appendix S1) and crossreferenced included reports.

131 Study selection

Titles and abstracts of identified reports were screened for eligibility; full text papers were retrieved if potentially eligible or unsure. All reports presenting causes of stillbirth were included to address Objective 1. To address Objectives 2 and 3, the most recent national report for each country was selected. If a national report was unavailable, a report was selected on criteria (in descending order): 1) population-based report with the largest number of stillbirths, 2) multi-centre health facility report covering the largest population.

138 Data extraction

A purpose built data extraction form was used. For details on data items and definitions used, seeAdditional Information S2.

141 Grouping reported stillbirth causes

The development of categories and mapping of reported causes of stillbirth to categories were undertaken by a panel including Maternal Fetal Medicine Specialists (GG, BS, DE), pathologist (RL) and epidemiologist (VF), with guidance from The Amsterdam Classification Workshop¹⁰ members. Categories were created by "clustering" reported causes into 15 clinically meaningful groups for stillbirth prevention ("global categories") (Table S1). With the addition of *Placental conditions*, these categories generally coincided with previously suggested major causal groupings by Lawn et al¹¹. We did not attempt to differentiate causes from associated conditions (Table S1).

149 Quality assessment

Quality assessment of country representative reports included in the pooled analysis of reported causes was performed using an adapted version of the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data¹² (Appendix S3). An overall quality rating was derived for each report (low, medium, or high quality). For subgroup analyses of "good" quality reports, we combined data from reports assessed as high and medium quality.

155 Data presentation and analysis

Data were presented by income setting using World Bank groupings¹³ of low and lower-middle (LIC; 156 Gross National Income (GNI) ≤\$3,955), upper-middle (MIC; GNI \$3,956- \$12,235) and high (HIC; 157 158 $GNI \geq 12,236$). Categories of stillbirth causes were presented as proportions of the total number of 159 stillbirths classified. Results from country representative reports were statistically pooled to identify 160 commonly reported causes stratified by country groupings. Analyses were done in R using the meta package¹⁴ with 95% prediction intervals (PI)¹⁵⁻¹⁷ (Appendix S4). Subgroup analyses by report quality 161 and type of system (ICD versus clinical classification systems) were planned a priori. See Appendix 162 S2 for definition of clinical classification systems⁶ and criteria for alignment of classification systems 163 164 with ICD-PM.

Each reported cause was mapped to the relevant ICD-PM major category. The ICD-PM includes five major maternal condition categories (M1-5) and 13 fetal categories, six with antepartum timing (A1-6) and seven with intrapartum timing $(I1-7)^4$. For the Unknown (U) timing category we included the 168 categories: U1: Congenital malformations, deformations and chromosomal abnormalities; U2:

169 Infection; U3: Other specified disorder; U4: Disorders related to fetal growth; U5: Death of

170 *unspecified cause.* We added one category, *Other*, to all timings to accommodate the causes without

171 ICD-PM coding.

172 The proportions of stillbirths that could be mapped to a fetal cause and/or a maternal condition in

173 ICD-PM were calculated. Mapping of data from good quality HIC reports to ICD-PM was compared

174 descriptively with the 15 global categories.

175 **Results**

Of 7415 abstracts screened for eligibility, 909 full-text papers were reviewed for inclusion and 824
records were excluded: did not discuss stillbirth (396), no extractable data (217), sub-populations
only (145), risk factors only (12) (for complete study selection see Figure S1). Eighty-five reports
(LIC 28, MIC 20, HIC 37) with a total of 489,089 stillbirths were included in the review (LIC 13,197,
MIC 431,216, HIC 44,676). Thirty-three country representative reports classifying 454,533 stillbirths
were included in the pooled analysis of causes and mapping to ICD-PM.

182 Global stillbirth reporting

183 Description of included reports

184 The 85 included reports originated from 50 countries. Reports were published in English (66) and

185 non-English (19; Table S2). Eleven reports excluded terminations of pregnancy. Half of the reports

- 186 (including 2.4% of all stillbirths) were from hospital settings (LIC: 19 reports/7419 stillbirths; MIC:
- 187 8 reports/1134 stillbirths; HIC: 16 reports/3240 stillbirths) (Table 1, for full details see Table S2).
- 188 Definitions of stillbirth
- 189 Stillbirth was defined in 71 reports (84%) using 34 discrete definitions (Figure S2). The majority of
- 190 HIC reports (78%) used a lower gestational age limit of 20-24 weeks while the majority of LIC reports
- 191 (68%) used 28 weeks (Table 1).
- 192 Data available to classifiers

193 Systematic prospective perinatal mortality audits were used in 21 reports (LIC 2, MIC 4, HIC 15), of 194 which 12 were hospital audits; seven used comprehensive investigation protocols (all from HIC) 195 (Table S2). In 40 reports, retrospective audit data were used; 18 of these (LIC 2, MIC 6, HIC 10) 196 sourced causes from Civil Registration and Vital Statistics (CRVS). Sixteen reports (LIC 13, MIC 3) 197 were prospective studies; eight of these, all from LIC, used verbal autopsy. Reported autopsy rates in 198 20 reports [MIC 3 (14%), HIC 17 (47%)] ranged from 2.7% to 100%. In over half of the reports 199 (55%) it was unclear whether autopsy had been performed. Placental pathology examination rates 200 were included in 15 reports (18%) (none in LIC) with rates ranging from 22% to 100%. For full 201 details on data available see Table S2.

202 Classification systems

Twenty-one clinical classification systems¹⁸⁻³⁸ were used in 41 of the 85 reports (LIC 15 reports/30% 203 204 of stillbirths, MIC 6 reports/5% of stillbirths, HIC 20 reports/27% of stillbirths). The ICD was used 205 more frequently in HIC (14 reports/72% of stillbirths) and MIC (7 reports/94% of stillbirths) than LIC (3 reports/2% of stillbirths) (Table 1). The remaining 20 reports listed causes of death without 206 207 reference to any classification system. Areas of origin for the 21 clinical systems is shown in Table 208 S3. Three-quarters of the systems allow a single primary cause of death, and half the systems allow 209 associated factors to be recorded (Table S4). Five systems provide comprehensive definitions of causes^{20,27,30-32} and 13 systems provide rules for assigning cause of death (See Table S4 for full details 210 211 on clinical classification systems).

212 Globally reported categories of stillbirth

The 85 included reports presented causes of stillbirth using 860 unique terms. These were grouped into 15 global categories and 46 minor categories, of which eight major categories were common to over half (53%) of the reports (Table S5).

Congenital anomalies was the most frequently reported category, included in 93% of all reports. The
 proportion of stillbirths assigned to this category ranged from 1.4% in Nigeria³⁹ to 64.4% in China⁴⁰
 (Figure 1, Table S5). The second category was *Unexplained*, included in 82% of all reports, ranging

- from 0.3% in Turkey²⁵ to 82.0% in Japan⁴¹. *Maternal conditions* were included in 64% of all reports,
- with frequency ranging from 0.6% in Ireland⁴² to 36.5% in Italy²⁸ (Figure 1, Table S5).
- 221 The proportions of categories also differed across type of classification system. The most commonly
- 222 reported categories for reports using the ICD included *Other unspecified condition* (68% of reports)
- 223 and Hypoxic peripartum death (64%), whereas for clinical systems these included Antepartum
- haemorrhage (72%) and Infection (67%).
- 225 Country representative reports
- 226 Description of included reports

Thirty-three reports classifying 454,533 stillbirths were included in the pooled analysis: seven LIC (5,629 stillbirths), 11 MIC (429,666 stillbirths), and 15 HIC (19,238 stillbirths). Twenty-one reports included \geq 95% of total stillbirths in the country during the reporting period, one report included 72%, three included 6-49% and eight included \leq 5% (Figure S3). In two reports (6%), terminations of pregnancy were excluded, and in 21 (64%), no reference was made to terminations. The ICD was used mainly in HIC and MIC reports (60% and 64%, respectively, versus 14% of LIC reports; Table 1, Table S2).

- 234 Quality assessment identified 13 good quality reports (29% of all LIC reports, 36% of all MIC reports,
- 47% of all HIC reports); only one of these was high-quality⁴³. The remaining reports were assessed
- as low-quality (Table S6, Figure S4).
- 237 Pooled estimates of commonly reported causes of stillbirths

The top five categories by frequency for each country grouping are shown in Figure 2. *Unexplained* was the top category across all settings, with pooled estimated ranging from 31.2% to 43.7% (Tables S7, S8). Two additional categories were amongst the top five across all settings: *Other unspecified conditions* (9.3% to 11.6%) and *Antepartum haemorrhage* (8.4% to 9.3%; Tables S7, S9, S10). In LIC, *Infection* (15.8%) and *Hypoxic peripartum death* (11.6%; Tables S7, S11, S12) were also amongst the top five. In both HIC and MIC settings *Placental conditions* (14.4% and 13.7%,

- 244 respectively) ranked in the top five, with Congenital anomalies as the remaining category in HIC
- 245 (14.0%) and *Specific fetal/pregnancy pathology* in MIC (11.0%) (Tables S7, S13, S14, S15).
- 246 Details of pooled analyses of Umbilical cord complications, Maternal conditions, Spontaneous
- 247 *preterm, Hypertension, Fetal growth restriction* and *Terminations* are presented in Tables S16-S21.
- 248 Sub-group analysis
- Due to insufficient data subgroup analysis by report quality was only possible for HIC. The proportion of *Unexplained* (15.4% vs 31.6%) and *Other unspecified conditions* (1.6% vs 9.3%) was lower in good quality reports versus all reports (Tables S8, S9). Subgroup analyses by system type showed higher proportions of *Antepartum haemorrhage* using clinical systems (14.1%) than using ICD (4.4%) in MIC (Table S10). Use of clinical systems resulted in lower proportions of *Other unspecified conditions* (1.6%) and *Unexplained* (17.7%) than use of ICD (13.2% and 43.4%, respectively) in HIC (Tables S9, S8).
- 256 Alignment with the ICD-PM
- 257 Alignment of clinical classification systems with the ICD-PM
- Of 21 classification systems used, only Codac¹⁹ was fully aligned with the ICD-PM. Four systems met two of the three criteria used to assess alignment, and 14 systems scored 0.5-1.5 out of a maximum of 3 (Table S3, Figure S5).
- 261 Mapping of reported causes to ICD-PM
- Nearly all the 454,533 stillbirths reported in the 33 country representative reports were mapped to an ICD-PM fetal or maternal category, or both. Causes for 831 stillbirths (0.2%) mapped to ICD-PM neonatal rather than fetal codes (for example "neonatal aspiration syndrome"). 264,480 stillbirths (58%) were mapped to a fetal but not a maternal ICD-PM cause, and 140,319 (31%) to a maternal but not a fetal ICD-PM cause; 49,734 stillbirths (11%) were mapped to both (Tables S22, S23).
- 267 Of the 204,545 stillbirths in the global category *Unexplained*, 113,558 (56%) were mapped to the
- 268 ICD-PM category Unknown timing unspecified (no maternal condition), 90,335 (44%) to Antepartum
- 269 *hypoxia* (no maternal condition), 602 (0.3%) to *Antepartum unspecified* (no maternal condition), and

50 (0.02%) to maternal condition *Other complications of labour and delivery* (no fetal cause) (Tables
S22, S23).

The global causes from best available data (good quality reports using clinical classification systems in HIC, five reports; 6,194 stillbirths) were mapped to ICD-PM. The global categories reflecting underlying placental causes of *Antepartum haemorrhage* and *Placental condition* (insufficiency) accounted for 20%, and *Intrauterine growth restriction* 7% of stillbirths (Figure 3). When mapped to the ICD-PM, these global categories are included within the major maternal category *Complications of placenta, cord and membranes* and the fetal category *Disorders related to fetal growth,* accounting for 30% and 17% of stillbirths, respectively (Figure 3).

279 **Discussion**

280 Main findings

From 85 reports presenting causes of nearly half a million stillbirths from 50 countries and all income settings, we identified 15 major causal categories from nearly 900 causal terms; eight categories were common to the majority of reports. Despite this overarching commonality, we found wide variation in frequency of stillbirth categories and in the systems used to classify them with generally poor quality data. Underlining one of the key challenges of achieving the Every Newborn Action Plan stillbirth target, are the high proportions of stillbirths without information to guide prevention (*Unexplained* and *Other unspecified conditions*) in all income settings.

288 Strengths and limitations

We sought to include the most detailed causes of stillbirth available to allow identification of common groupings, and ultimately to enable consistent reporting across settings. In line with WHO recommendations^{4,44} and to maximize the utility of the data for prevention strategies, we excluded reports which assigned more than one cause of stillbirths and excluded all those reported as associated only. This may have resulted in a loss of information and limited our ability to assess the full value of the ICD-PM, which aim to record both a fetal and a maternal condition for every stillbirth. The need to assign multiple causes for some stillbirths has been highlighted. Further, the distinction between causes and associated conditions is often poorly defined²⁶ and in this review many reported "causes" are not recognised as causal conditions. Further, although we imposed no language restriction, we may have missed some reports due to English-language search terms.

299 Interpretation

300 Data quality

Data quality was generally poor with only a small number of reports based on high quality perinatal mortality audit. Further, many reports did not provide sufficient detail to adequately assess quality. Similar to others^{1,5,45}, we found global comparisons problematic due to differing definitions and systems. The inability to identify termination of pregnancies in reporting of stillbirth causes is problematic; many are terminated as a consequence of congenital anomalies⁴⁶, some of which may not have resulted in stillbirth.

307 Global causes of stillbirth

308 Results of the pooled analysis enabled comparisons of stillbirth causes across settings, providing additional evidence for key areas for prevention. The relatively high proportion of stillbirths attributed 309 310 to intrapartum hypoxia (Hypoxic peripartum) in LIC versus HIC and MIC is in line with recent evidence from low- and middle-income countries (LMIC)^{47,48} and confirms the urgency of improving 311 care during labour and birth, when half of all global stillbirths occur^{1,3,47,49}. Further, similar to other 312 reports^{47,48} we identified infection as a top cause of stillbirths in LIC, confirming the importance of 313 infection prevention and management^{3,49,50}. Our findings clearly highlight the importance of placental 314 conditions as a major contributor to stillbirths in all settings, consistent with other recent studies^{47,51}. 315 316 However, many placental conditions were ill-defined and the causal link unclear (for instance delayed villous maturation)^{52,53}. Many conditions that lead to stillbirth are also linked to neonatal deaths and 317 318 therefore both must be accommodated within a single system to ensure optimal pregnancy care and outcomes⁵⁴. 319

320 *ICD-PM and progress towards global reporting*

321 We confirmed findings of other studies, showing numerous disparate systems for classification of 322 stillbirths in use globally^{5,45,55}, further highlighting the need for a globally effective classification system. A recent consensus described user-identified characteristics for such a system⁵⁶, however no 323 existing systems meet these characteristics⁵⁷. Further, robust evaluation of system performance is 324 limited⁶. The ICD-PM is the first system intended for global use in classification of perinatal 325 deaths^{4,58-60}, aiming to facilitate comparisons by improving perinatal mortality data, particularly in 326 327 high burden settings. While evaluation of the performance of ICD-PM is currently limited, 328 retrospective application to datasets in the UK and South Africa highlighted its values and provided insights to future improvements⁵⁹. In our dataset, all causes of stillbirths reported globally could be 329 330 accommodated within the ICD-PM. However, our mapping of causes from good quality reports in 331 HIC using clinical classification systems highlights that classification system needs differ across 332 settings. Meeting the needs of diverse settings is essential for global comparisons to identify important 333 variation and inform programmatic change to reduce deaths.

The WHO Perinatal Mortality Audit and Review guide⁷ provides a tool to initialize audits in low-334 income settings using the ICD-PM for classifying perinatal deaths. The ICD-PM maps ICD-10 codes 335 to an underlying fetal cause of antepartum, intrapartum or unknown timing, and a maternal condition; 336 337 thus, data collection must include timing as well as fetal and a maternal condition. While this approach 338 aims to capture information on stillbirths from low resource settings (either cause and/or associated conditions) the ICD-PM faces challenges due to its ICD-10 provenance, including insufficient 339 340 differentiation of causes from associated conditions, and insufficient detail on maternal conditions⁸. 341 Conditions noted as Maternal in the ICD-PM include not only fetal underlying causes (Placenta, cord 342 and membranes), but also maternal causes (Maternal complications of pregnancy) and maternal 343 associated conditions (Maternal medical and surgical conditions). Further, one-fifth of stillbirths in 344 the global category Unexplained mapped to ICD-PM Antepartum asphyxia. Classifying associated conditions is important, particularly in data poor settings where assigning cause may be difficult. 345 346 However confusing causes from associated conditions or mechanisms of deaths (antepartum

asphyxia) while reducing the number of *Unexplained*, may obscure key areas for prevention. WHO
is currently working towards ICD-11 which provides an opportunity to alleviate some of these
issues[World Health Organization, #269].

350 Differences in proportions of causal categories across countries, were likely due to different classification approaches. Codac¹⁹ was the only non-ICD system fully aligned with the ICD-PM. 351 Although Codac has previously been shown to be the best-performing system⁴⁵, the majority of 352 353 stillbirths classified using Codac were mapped to unknown timing and cause within the ICD-PM (data 354 not shown). Codac also resulted in a high proportion of Unexplained stillbirths, potentially influenced 355 by the categories included. Moreover, this system was only aligned with nine of the 17 user-identified 356 characteristics for an effective global system. Future enhancements to global classification of 357 stillbirths need to incorporate user-identified characteristics for an effective global system. Further, 358 optimisation of information from data-rich settings to incorporate recent advances in stillbirth 359 aetiology such as the consensus on placental pathology⁵³, and other detailed laboratory investigations 360 will serve to advance prevention of stillbirths globally. Implementation of any system must also be 361 accompanied by appropriate training to ensure high-quality data.

362 Conclusion

To achieve the Every Newborn Action Plan global stillbirth rate target, improving care of women in 363 364 labour and birth and preventing and treating infections and the quality of data on causes to drive 365 change are priorities. Implementation of ICD-PM as part of the WHO Perinatal Mortality Audit and 366 Review guide⁷ would be a major step forward. While the ICD-PM captures data from high-burden settings by allowing for a minimum of timing and clinically defined causes and associated conditions, 367 368 a global system must also accommodate needs of data-rich settings to enable global comparisons. 369 Clearly ascertaining underlying causes separate from associated conditions and enabling capture of 370 more detailed information in data-rich settings will fully harness the ICD-PM's potential for global 371 reporting and prevention of stillbirths. Further research is needed to improve the classification of

372 placental causes of stillbirths. Enhancements to global classification of stillbirths and neonatal deaths

373 must be based on comprehensive testing across diverse settings.

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380 Disclosure of Interests

381 GS receives/has received research support from GE (supply of two diagnostic ultrasound systems), 382 from Roche (supply of equipment and reagents for biomarker studies, value £596,142) and from GSK 383 (£199,413 for in vitro studies on human myometrium). GS has been paid to attend advisory boards 384 by GSK and Roche. GS has acted as a paid consultant to GSK. GS has received support to attend a 385 scientific meeting from Chiesi. GS is named inventor in a patent submitted by GSK for a novel application of an existing GSK compound for the prevention of preterm birth (PCT/EP2014/062602). 386 387 GS was a member of a GSK Data Safety Monitoring Committee for a trial of RSV vaccination in 388 pregnancy and infancy, 2016-2017.

389 **Contribution to Authorship**

390 HR was responsible for the conduct of the study. VF conceptualized the study and developed methods 391 and procedures with HR, MC and SHL. HR, VF, SHL, AW and ZT undertook searches, selection of 392 studies, data extraction and quality assessment. GG, DE, RL and VF created the global stillbirth 393 categories. MC oversaw all statistical aspects of the study and undertook the pooled analysis. VF and 394 SHL undertook the assessment of ICD-PM alignment with advice from RP, JG, ÖT and EA. HR and 395 VF were responsible for interpretation of findings and preparation of the first draft of the manuscript.

396	SH, AW, GG, RL, DE, ZT, EA, HB, ED, JJE, FF, JG, KG, SG, AG, AH, YK, FK, JL, EM, JO, RP,
397	KP, DS, RS, GS and ÖT have been actively involved throughout planning and consultation stages of
398	the project and provided comments on the manuscript. HR, SHL, MC, SH, AW, GG, RL, DE, ZT,
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