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## Miscarriage matters

*the epidemiological, physical, psychological, and economic costs of early pregnancy loss*

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1 Miscarriage matters: the epidemiological, physical, psychological and economic  
2 burden of early pregnancy loss

3  
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37 **Summary**

38 Miscarriage is generally defined as the loss of a pregnancy before viability. An estimated 23 million  
39 miscarriages occur every year worldwide, translating to 44 pregnancy losses each minute. The  
40 pooled risk of miscarriage is 15.3% (95% CI: 12.5% – 18.7%) of all recognised pregnancies. The  
41 population prevalence of women with one miscarriage is 10.8% (95% CI 10.3% – 11.4%), two  
42 miscarriages is 1.9% (95% CI 1.8% – 2.1%) and three or more miscarriages is 0.7% (0.5% – 0.8%).  
43 Risk factors for miscarriage include very young or older female age, older male age, very low or very  
44 high body mass index, black ethnicity, previous miscarriages, smoking, alcohol, stress levels, night  
45 shift working, air pollution and exposure to pesticides. The consequences of miscarriage are both  
46 physical, such as bleeding or infection, and psychological.  
47 Psychological consequences include increases in the risk of anxiety, depression, post-traumatic  
48 stress disorder and suicide. Miscarriage, and especially recurrent miscarriage, is also a sentinel risk  
49 marker for obstetric complications, including preterm birth, fetal growth restriction, placental  
50 abruption and stillbirth in future pregnancies, and a predictor of longer-term health problems, such  
51 as cardiovascular disease and venous thromboembolism.  
52 The costs of miscarriage affect individuals, healthcare systems and society at large. The short-term  
53 national economic cost of miscarriage is estimated to be £471 million per year in the United  
54 Kingdom. As recurrent miscarriage is a sentinel marker for various obstetric risks in future  
55 pregnancies, women should receive care in pre-conception and high-risk obstetric clinics. As  
56 psychological morbidity is common after pregnancy loss, effective screening instruments and  
57 treatment options for mental health consequences of miscarriage need to be available. We  
58 recommend that miscarriage data are gathered and reported to facilitate comparison of rates  
59 amongst countries, to accelerate research, and to improve patient care and policy development.

60

61 **Keywords:** miscarriage, epidemiology, risk, prevalence, economic burden, literature review

62

63

64 **Introduction**

65 Miscarriage is often misunderstood by women, men,<sup>1</sup> and healthcare providers. Misconceptions  
66 about miscarriage are widespread.<sup>1-3</sup> For example, women may believe miscarriage is rare, could be  
67 caused by lifting heavy objects or previous contraceptive use, or that there are no effective  
68 treatments to prevent a miscarriage.<sup>3</sup> Such misconceptions can be damaging, leaving women and  
69 their partners feeling at fault and not seeking treatment and support.<sup>1</sup> Miscarriage may also lead to  
70 isolation, since many women may not tell their family, close friends, or even their partner about the  
71 loss. Couples complain of unsympathetic 'routine' clinical care by healthcare providers.<sup>4-6</sup>  
72 Women and their partners who suffer miscarriage generally want to understand why the miscarriage  
73 occurred, what they can do to prevent miscarriage from happening again, what the chance is of a  
74 subsequent pregnancy resulting in a healthy baby and how to deal with their grief surrounding their  
75 loss.<sup>3</sup> Couples may be given diverse opinions by different healthcare professionals, which can  
76 exacerbate their distress. There are debates over definitions, causes, consequences and costs of  
77 miscarriage. This is the first of three articles in which we present the current knowledge,  
78 recommendations, need for further research and a call to action on priorities. Here we discuss the  
79 epidemiology of sporadic and recurrent miscarriage, and present a literature review of the risk  
80 factors and consequences of miscarriage on future obstetric and maternal psychological and long-  
81 term health. We also evaluate the economic burden of miscarriage through a review of the  
82 literature.

83

84 **Box 1:** Methods for literature searches for miscarriage risk, prevalence, risk factors and  
85 consequences

We performed a comprehensive literature search on MEDLINE (database inception to May 2020).

We searched for existing systematic reviews and primary studies on risk factors for miscarriage

(demographic, lifestyle, clinical and environmental factors). A separate search was conducted for observational studies of obstetric, perinatal and long-term health risks associated with miscarriage. Free text search terms and Medical Subject Headings (MeSH) terms for miscarriage were combined with each risk factor, pregnancy sequelae, perinatal and long-term health outcome. For each literature review, the raw aggregate data or adjusted odds ratios were presented.

86

### 87 **Definitions and terminology**

88 The definition of miscarriage varies amongst countries, and international organisations, impacting  
89 upon estimations of the risk and prevalence of miscarriage. Miscarriage is generally defined as the  
90 loss of an intrauterine pregnancy before viability; however, challenges exist over the diagnosis of  
91 pregnancy, and the definitions of what is unequivocally an intrauterine pregnancy and viability. The  
92 limits of viability may be defined by gestational age or by fetal weight. The gestational threshold for  
93 viability can range from 20 to 28 weeks of pregnancy depending on geographical region. The World  
94 Health Organization defines miscarriage as the expulsion of a fetus (embryo) weighing less than 500  
95 grams, equivalent to approximately 22 weeks of gestation.<sup>19</sup> In the UK the limit of viability is  
96 determined legally as up to 24+0 weeks.<sup>18</sup> The American Society for Reproductive Medicine (ASRM)  
97 defines miscarriage as a clinical pregnancy loss of less than 20 weeks of gestation.<sup>20</sup> The European  
98 Society for Human Reproduction and Embryology (ESHRE) defines miscarriage as the loss of  
99 pregnancy before 22 weeks of gestation.<sup>21</sup> The limit of viability is, in most nations, legally defined  
100 and, particularly as neonatal intensive care for preterm infants becomes more effective in high  
101 income countries, often deviates from the medical limits of viability. Whilst embryologists define the  
102 first week of pregnancy as the week following implantation, historically, for clinical purposes  
103 'gestational age' has referred to the length of pregnancy after the first day of the last menstrual  
104 period. That convention will be used in this review.

105 A bewildering array of terminology for pregnancy failure before viability has developed based upon  
 106 whether the pregnancy diagnosis was based on serum or urinary  $\beta$ -hCG levels, or on the visualisation  
 107 of an intrauterine pregnancy by ultrasonography (Table 1).

108

109 **Table 1.** Early pregnancy terminology

Term	Description
Pregnancy loss	Spontaneous pregnancy demise
Early pregnancy loss	Spontaneous pregnancy demise before 10 weeks of gestational age
Biochemical pregnancy Loss	Spontaneous pregnancy demise based on a previous positive pregnancy test that then becomes negative without an ultrasound evaluation
Pre-clinical pregnancy loss	Loss of a pregnancy before it could be identified on TVS
Clinical pregnancy loss	Loss of a pregnancy after it has been identified on TVS
Pregnancy of unknown location (PUL)	Temporary classification to describe when no pregnancy can be visualised inside or outside the uterus on TVS in a woman with a positive pregnancy test
Resolved pregnancy loss of unknown location (Resolved PUL)	Following the finding of a PUL, the woman has a negative pregnancy test 2 weeks after her initial follow-up
Persistent pregnancy of unknown location (PPUL)	Following the finding of a PUL, serial serum human chorionic gonadotropin (hCG) levels taken 48 hours apart plateau, while the location of the pregnancy remains unclear using TVS.
Intrauterine pregnancy of unknown viability (IPUV)	TVS has shown the following, irrespective of the date of a woman's last menstrual period: <ul style="list-style-type: none"> <li>- intrauterine gestational sac seen with an MSD of &lt;25 mm without a visible yolk sac or embryonic pole</li> <li>- intrauterine gestational sac with MSD of &lt;25 mm with a yolk sac seen without a visible embryonic pole</li> <li>- intrauterine gestational sac with an embryo with a CRL measuring &lt;7 mm with no visible heartbeat</li> </ul>
Viable intrauterine pregnancy (VIUP)	Intrauterine gestational sac containing an embryo with a heartbeat that has been visualised using ultrasonography
Miscarriage	Intrauterine pregnancy demise confirmed by TVS or histology of pregnancy tissue
Missed miscarriage	An intrauterine pregnancy with an empty gestational sac of $\geq$ MSD 25 mm, or an embryo with an embryo CRL measurement of >7 mm without an embryonic heartbeat

Incomplete miscarriage	Irregular heterogeneous echoes within the endometrial cavity on TVS and the diagnosis is based on the subjective impression of the examiner and the clinical findings
Complete miscarriage	History of a positive pregnancy test followed by vaginal bleeding (or a history of an ultrasound scan demonstrating an IUP) and then an ultrasound finding of an empty uterine cavity with no intra or extra-uterine pregnancy visualised on TVS with a negative pregnancy test

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TVS: transvaginal ultrasound scan; IU(P): intrauterine (pregnancy); MSD: mean sac diameter; CRL: crown-rump length. Table adapted from 'Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group'<sup>22</sup> and Doubilet et al, 2013.<sup>23</sup>

### 115 Risk of miscarriage

116 The risk of miscarriage depends both upon the defined upper gestational age or fetal weight limit,  
117 and upon whether the denominator is all pregnancies identified by serum or urinary  $\beta$ -hCG levels or  
118 only pregnancies diagnosed by ultrasonography. Inclusion of pre-clinical losses, defined as the loss of  
119 a pregnancy before it could be identified on ultrasonography, will increase the miscarriage rate. The  
120 development of highly sensitive  $\beta$ -hCG assays has allowed detection of very early pregnancies, and  
121 therefore diagnosis of very early miscarriages which otherwise may have been missed, again  
122 resulting in an increase in the miscarriage rate. Finally, demographic features of a population will  
123 affect the miscarriage risk, with the distribution of female age having a profound effect on the risk.  
124 Our literature search identified nine large cohort studies that reported on miscarriage risk in an  
125 aggregated total of 4,638,974 pregnancies (Table 2).<sup>24-31</sup> All the studies were from Europe and North  
126 America. Six studies were prospective cohorts using self-reported pregnancy outcomes, and three  
127 used record linkage, to ascertain the outcome of miscarriage. Our review of current evidence found  
128 that the pooled miscarriage risk was 15.3% (95% CI: 12.5% – 18.7%) of all recognised pregnancies  
129 (Table 2).

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131  
132

133 **Table 2.** Risk of miscarriage in pregnant women



Study	Source population	Definition of miscarriage	Miscarriages / pregnancies	Miscarriage risk (%) (95% CI)
<b>Himmelberger et al, 1978</b>	Survey of operating room personnel in the USA from 1972 to 1974	Self-reported pregnancy outcomes	2,157 / 12,914	16.7 (16.0, 17.4)
<b>Armstrong et al, 1992</b>	Women with a reproductive outcome at 11 hospitals in Montreal, Canada from 1982 to 1984	Self-reported pregnancy outcomes	10,191 / 47,146	21.6 (21.2, 22.0)
<b>Andersen et al, 2000</b>	Women with a reproductive outcome in Denmark from 1978 to 1992	Record linkage using a National Hospital Discharge Registry and excluding ectopic pregnancies. Induced abortions were excluded through linkage with an induced abortion register	85,838 / 936,524	9.2 (9.1, 9.2)
<b>Adolfsson and Larsson, 2006</b>	Women with a reproductive outcome in Sweden from 1983 and 2003	Self-reported pregnancy outcomes for all women who delivered a child	366,796 / 2,136,809	17.2 (17.1, 17.2)
<b>Maconochie et al, 2006</b>	Survey of reproductive histories of women randomly sampled from the UK electoral register in 2001	Self-reported pregnancy outcomes	1,322 / 8,523	15.5 (14.7, 16.5)
<b>Linnakaari et al, 2019</b>	Nationwide retrospective cohort study of women that had experienced a miscarriage in Finland between 1998 and 2016	Record linkage using ICD codes in National Hospital Discharge Registry database and excluding codes of ectopic pregnancy, molar pregnancy, induced abortions or continuing pregnancy	128,381 / 1,096,916	11.7 (11.6, 11.8)
<b>Magnus et al, 2019</b>	Women with a reproductive outcome in Norway from 2009 to 2013	Record linkage using ICD codes in National Birth Registry and patient register excluding ectopic pregnancies. Induced abortions were excluded through linkage with an induced abortion register	43,803 / 344,906	12.7 (12.6, 12.8)
<b>Rossen et al, 2019</b>	National survey of women who reported at least one pregnancy that was conceived in the USA between 1990 and 2011	Self-reported pregnancy outcomes	8,378 / 42,526	19.7 (19.3, 20.1)
<b>Nguyen et al, 2019</b>	National survey of women who reported pregnancy outcomes that was conceived in the USA between 2011 and 2015	Self-reported pregnancy outcomes	2,300 / 12,710	18.1 (17.4, 18.9)

<b>Pooled risk</b>	15.3 (12.5, 18.7)
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136 With approximate 130 million births per year worldwide<sup>32</sup>, a 15% miscarriage risk suggests  
 137 approximately 23 million miscarriages per year, or 44 per minute. In the UK, there were 40-45,000  
 138 hospital admissions in 2012-2013 for miscarriage management,<sup>33</sup> but since miscarriages and  
 139 preclinical pregnancy losses are commonly managed at home, the actual number of miscarriages is  
 140 considerably higher. Unfortunately, since 2013 the data on hospital admissions for miscarriage are  
 141 no longer included in the UK maternity statistic report.<sup>33</sup> Only a few countries, for example Denmark,  
 142 report an annual miscarriage rate, which makes international comparisons difficult. Based on limited  
 143 cohort studies, the incidence of miscarriage appears to be increasing in the USA,<sup>30</sup> China<sup>34</sup> and  
 144 Sweden<sup>35</sup>, but decreasing in Finland.<sup>28</sup> The reasons for these changes are not clear but may reflect  
 145 increasing female age at the time of pregnancy. Female age and the number of previous  
 146 miscarriages have a profound effect on miscarriage risk (Table 3). Miscarriage risk is the lowest in  
 147 women aged 20 – 29 years at 12%, increasing steeply to 65% in women aged 45 years and over  
 148 (Table 3). The miscarriage risk is the lowest women with no history of miscarriage (11%), and then  
 149 increases by about 10% for each additional miscarriage, reaching 42% in women with 3 or more  
 150 previous miscarriages (Table 3).

151

152 **Table 3.** Miscarriage risk according to female age and number of previous miscarriages

	Number of studies	Miscarriages / pregnancies	Miscarriage risk (%) (95% CI)
<b>Age category (years)</b>			
<20	4	9,165 / 71,763	15.9 (11.3, 22.4)
20-24	3	32,326 / 337,995	12.1 (8.5, 17.2)
25-29	6	47,266 / 481,112	11.9 (10.0, 14.3)
30-34	6	37,015 / 309,328	14.4 (11.4, 18.2)
35-39	4	21,607 / 118,771	17.9 (15.8, 20.2)
40-44	2	8,635 / 23,783	36.8 (30.1, 45.0)
≥45	2	1,081 / 1,687	65.2 (49.8, 85.2)
<b>Number of previous miscarriages</b>			
0	3	23,233 / 172,405	11.3 (7.2, 17.6)
1	3	6,770 / 31,564	20.4 (13.8, 30.3)

<b>2</b>	3	1,276 / 4,221	28.3 (19.0, 42.1)
<b>≥3</b>	3	364 / 865	42.1 (38.0, 46.7)

153

154

155 **Recurrent miscarriage**

156 Whether miscarriage should be defined as recurrent after two or more, or three or more pregnancy

157 losses is an ongoing controversy. There is also no consensus on whether recurrent miscarriage

158 should be restricted to clinical losses only or include both clinical and pre-clinical losses (Table 4).

159 The definitions are further complicated by whether the previous pregnancy losses need to be

160 consecutive or may be interspersed with successful pregnancies. The UK Royal College of

161 Obstetricians and Gynaecologists (RCOG) defines recurrent miscarriage as the loss of three or more

162 consecutive pregnancies. However, in this definition, the term 'miscarriage' encompasses all

163 pregnancy losses from the time of conception until 24 weeks, including biochemical pregnancy

164 losses and failed pregnancies of unknown location. The German, Austrian and Swiss Societies of

165 Gynaecology and Obstetrics offer similar guidance. The American Society for Reproductive Medicine

166 (ASRM) has defined recurrent miscarriage as 'two or more failed clinical pregnancies'. Since the

167 diagnosis of pregnancy in this definition requires ultrasound or histological confirmation, it excludes

168 biochemical pregnancy losses and failed pregnancies of unknown location. The European Society of

169 Human Reproduction and Embryology (ESHRE) have recently redefined recurrent pregnancy loss as

170 two or more pregnancy losses without the stipulation that these need to be consecutive. This

171 definition would therefore apply even if there had been a successful pregnancy in between

172 pregnancy losses. These variations in the definition of recurrent miscarriage or recurrent pregnancy

173 loss have important implications on the reported prevalence, and on the prognosis in any future

174 pregnancy. The average population prevalence of women with one previous miscarriage is 10.8%,

175 two miscarriages is 1.9% and three or more miscarriages is 0.7% (Figure 7). If two or more pregnancy

176 losses is adopted as the definition of recurrent miscarriage, the population prevalence of recurrent

177 miscarriage equates to 2.6%. The chance of a future successful subsequent pregnancy ranges from

178 50 to 90%, depending on the recurrent miscarriage definition used and population characteristics.<sup>36-</sup>

179 <sup>43</sup>

180

181 **Table 4.** Differences in definition of recurrent miscarriage amongst national guidelines

Guidelines	UK (RCOG) <sup>44</sup>	USA (ASRM) <sup>20</sup>	Europe (ESHRE) <sup>21</sup>	Japan <sup>45</sup>	German, Austrian and Swiss Societies of Gynaecology and Obstetrics <sup>46</sup>
Definition of pregnancy loss	Includes clinical and pre-clinical losses	Includes clinical losses only (identified on ultrasound or histology)	Includes clinical and pre-clinical losses	Includes clinical losses only (identified on ultrasound or histology)	Includes clinical losses only (identified on ultrasound or histology)
Number previous of losses	≥3	≥2	≥2	≥2	≥3
Consecutive losses	Yes	No	No	No	Yes

182

183 **Table 7.** Population prevalence of miscarriage

	Miscarriages / women	Prevalence of miscarriage (%) (95% CI)
<b>1 miscarriage</b>		
Hemminki and Forssas, 1999	193 / 2,189	8.8 (7.7, 10.2)
Oliver-Williams and Steer, 2015	21,658 / 196,040	11.0 (10.9, 11.2)
Woolner et al, 2019	3,513 / 31,565	11.1 (10.8, 11.5)
	<b>Sub-total</b>	10.8 (10.3, 11.4)
<b>2 miscarriages</b>		
Hemminki and Forssas, 1999	57 / 2,189	2.6 (2.0, 3.4)
Oliver-Williams and Steer, 2015	3,624 / 196,040	1.8 (1.8, 1.9)
Woolner et al, 2019	590 / 31,565	1.9 (1.7, 2.0)
	<b>Sub-total</b>	1.9 (1.8, 2.1)
<b>3 miscarriages</b>		
Hemminki and Forssas, 1999	22 / 2,189	1.0 (0.7, 1.5)
Oliver-Williams and Steer, 2015	1,426 / 196,040	0.7 (0.7, 0.8)
<b>Roepke et al, 2017</b>	7,842 / 1,524,130	0.5 (0.5, 0.5)
Woolner et al, 2019	181 / 31,565	0.6 (0.5, 0.7)
	<b>Sub-total</b>	0.7 (0.5, 0.8)

184

185

186 The current definitions of recurrent miscarriage do not go beyond the inclusion or exclusion of pre-  
187 clinical losses and the setting of an arbitrary number of prior losses. However, the risk of miscarriage  
188 increases independently with maternal age and with the number of previous losses (Table 3). A  
189 definition of recurrent miscarriage that is based on individualised risk assessment which takes into  
190 account maternal age, reproductive history, and other clinical variables is likely to facilitate better  
191 stratification, targeted care and research.

192

### 193 **Risk factors for miscarriage**

#### 194 *Embryonic chromosomal errors*

195 Chromosomal abnormalities are found in 60% of miscarried tissue<sup>47</sup> but less than 1% of live births,  
196 when pre-natal diagnosis is not used.<sup>48</sup> Amongst miscarriages, autosomal trisomy is the most  
197 frequent abnormality followed by monosomy X and triploidy.<sup>47</sup> In addition, developmental  
198 abnormalities of embryos not seen in live births are found in miscarriages with normal  
199 chromosomes.<sup>49,50</sup>

200

#### 201 *Endometrial defects*

202 Endometrium transforms into decidua during implantation to accommodate the invading placenta.<sup>51</sup>  
203 A defect in decidualization can result from changes in immune cells,<sup>52</sup> foremost uterine natural killer  
204 cells,<sup>53</sup> or endometrial stem cells,<sup>54,55</sup> which may result in endometrial breakdown and miscarriage.  
205 Multiple risk factors of recurrent miscarriage, including metabolic (e.g. obesity) and endocrine (e.g.  
206 hypothyroidism) disorders (Table 6), have been shown to impact adversely on the decidual process  
207 in the endometrium.<sup>57,58</sup>

208

#### 209 *Parental risk factors of miscarriage*

210 There are demographic, lifestyle, clinical and environmental risk factors for miscarriage (Table 6).

211 The inferences about the risk factors are based on the strength of association (represented by the

212 size of odds ratios), consistency amongst the studies, biological gradient, and the persistence of  
213 association after adjustments for key confounding variables, particularly female age.<sup>59</sup>

214

#### 215 *Demographic risk factors*

216 Our literature review showed that the key demographic risk factors for miscarriage are female age,  
217 female body mass index (BMI), female ethnicity and male age (Table 6). There is a strong association  
218 between female age and miscarriage risk, with a powerful biological gradient, found consistently in  
219 several studies (Table 6). This association is attributed to an age-related increase in the frequency of  
220 embryonic trisomies, particularly trisomy 13, 14, 15, 16, 18, 20, 21, and 22.<sup>60,61</sup> The risk of trisomy  
221 16, the commonest cause of miscarriage, rises linearly from 20 years to 40 years of age, whilst the  
222 risks of other trisomies generally show a sharp upward inflection around the age of 35 years.<sup>47</sup> Our  
223 literature searches found that female BMI is associated with miscarriage risk; the BMI associated  
224 with the least risk of miscarriage is 18.5 – 24.9 kg/m<sup>2</sup> (Table 6). Black ethnicity is associated with a  
225 higher risk (aOR 1.64; 95% CI 1.07-2.49; Table 6), as is male age of ≥40 years, even after adjusting for  
226 confounders such as the age of female partner (aOR 1.61; 95% CI 1.27 – 2.03; Table 6).

227

228

229 **Table 6.** Demographic, lifestyle, clinical and environmental risk factors for miscarriage

	Crude estimates		Adjusted estimates	
	Number of women (studies)	Odds ratio [95% CI]	Number of women (studies)	Odds ratio [95% CI]
<b>Demographic risks</b>				
<b>Female age</b>				
<20 years of age	1,132,164 (6)	1.60 [1.02, 2.53]	273,209 (2)	1.47 [0.94, 2.30]
20-29 years of age	-	Reference	-	Reference
30-39 years of age	1,709,852 (3)	1.43 [1.13, 1.81]	273,209 (2)	1.54 [1.23, 1.93]
≥40 years of age	1,030,387 (3)	6.43 [4.69, 8.82]	273,209 (2)	5.85 [3.67, 9.34]
<b>Male age</b>				
<20 years of age	20,808 (5)	0.87 [0.62, 1.21]	12,794 (3)	1.12 [0.81, 1.55]
20-29 years of age	-	Reference	-	Reference
30-39 years of age	29,795 (6)	1.23 [0.95, 1.60]	539 (1)	1.14 [0.75, 1.74]
≥40 years of age	16,108 (6)	1.69 [1.18, 2.43]	6,875 (2)	1.61 [1.27, 2.03]
<b>BMI</b>				
<18.5	117,936 (11)	1.57 [1.05, 2.34]	74,324 (7)	1.21 [0.96, 1.52]
18.5-24.9	-	Reference	-	Reference
25-29	131,896 (10)	1.33 [1.10, 1.59]	88,286 (6)	1.04 [0.91, 1.18]
≥30	118,102 (10)	1.93 [1.18, 3.18]	74,362 (4)	1.09 [0.99, 1.21]
<b>Ethnicity</b>				
Caucasian	-	Reference	-	Reference
Black	504,224 (19)	1.43 [1.17, 1.75]	88,286 (6)	1.64 [1.07, 2.49]
Asian	415,207 (13)	1.27 [0.99, 1.63]	74,362 (4)	1.25 [0.90, 1.75]
<b>Lifestyle Risks</b>				
<b>Smoking</b>				
Current smoking and in the first trimester	281,689 (29)	1.30 [1.20, 1.41]	265,827 (8)	1.17 [1.05, 1.30]
<b>Caffeine</b>				
High caffeine intake during the first trimester	45,990 (3)	1.26 [1.05, 1.51]	128,900 (3)	1.56 [0.98, 2.50]
<b>Alcohol</b>				
High alcohol intake during the first trimester	170,856 (17)	1.29 [1.16, 1.43]	152,881 (11)	1.67 [1.31, 2.19]
<b>Work pattern</b>				
Overworking (>40 hours per week)	16,315 (4)	1.93 [1.16, 3.21]	14,760 (4)	1.26 [0.94, 1.70]
Night shifts	74,011 (6)	1.31 [1.14, 1.50]	74,011 (6)	1.46 [1.25, 1.71]
<b>Stress</b>				
High stress	23,393 (5)	1.35 [1.18, 1.56]	29,498 (7)	1.43 [1.16, 1.77]

<b>Clinical Risks</b>				
<b>Previous miscarriages</b>				
No previous miscarriage	-	Reference	-	Reference
1 previous miscarriage	347,292 (12)	1.69 [1.49, 1.91]	209,168 (6)	1.54 [1.46, 1.62]
2 previous miscarriages	254,575 (6)	2.24 [1.62, 3.10]	177,596 (4)	2.21 [2.08, 2.34]
3 or more previous miscarriages	249,384 (6)	4.13 [2.62, 6.52]	174,252 (4)	4.46 [3.48, 5.72]
<b>DNA damage</b>				
High DNA damage in sperm	1,252 (16)	2.67 [1.67, 4.28]	-	-
<b>Thyroid disease</b>				
Thyroid antibodies	7,946 (17)	2.29 [1.86, 2.81]	3,202 (2)	2.95 [1.71, 5.11]
Subclinical hypothyroidism (TSH 2.5-5.0mIU/L)	188,736 (7)	1.58 [1.18, 2.12]	181,978 (3)	1.35 [0.97, 1.89]
Subclinical hypothyroidism (TSH 4.0-10.0mIU/L)	159,194 (7)	1.64 [1.46, 1.85]	154,232 (2)	1.93 [1.17, 3.18]
<b>Uterine anomalies</b>				
Septum defects	2,695 (4)	3.93 [2.57, 6.01]	-	-
Mullerian anomalies	970 (3)	3.20 [0.93, 10.98]	-	-
Fibroids	23,864 (32)	1.42 [1.24, 1.63]	6,057 (3)	0.82 [0.64, 1.05]
<b>Polycystic ovary syndrome</b>				
Polycystic ovary syndrome	22,235 (27)	1.33 [1.05, 1.68]	2,418 (2)	0.97 [0.64, 1.45]
<b>Thrombophilia</b>				
Acquired (Antiphospholipid syndrome)	10,781 (13)	2.28 [1.46, 3.57]	-	-
Inherited (Factor V Leiden, Protein S deficiency, Protein C deficiency, Antithrombin III deficiency, Prothrombin deficiency)	36,758 (12)	1.12 [0.93, 1.36]	18,395 (4)	1.29 [0.90, 1.85]
<b>Parental Karyotype</b>				
Abnormal parental karyotype (any)	2,569 (3)	2.20 [1.09, 4.42]	-	-
<b>Environmental risks</b>				
<b>Air pollution</b>				
Industrial pollution	15,177 (4)	1.58 [1.08, 2.29]	20,044 (4)	1.54 [1.03, 2.31]
Household pollution	1,125 (2)	1.11 [0.22, 5.50]	819 (1)	2.10 [0.91, 4.81]
<b>Pesticides</b>				
Exposure to pesticides	20,729 (8)	1.71 [1.24, 2.37]	10,407 (4)	3.40 [1.20, 9.63]

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234 *Lifestyle risk factors*

235 Smoking is an important modifiable risk factor for miscarriage (Table 6). The risk is greater when  
236 smoking exposure occurs specifically during the pregnancy in which miscarriage risk was measured.<sup>41</sup>  
237 Miscarriage risk increases with the amount smoked (1% increase in relative risk per cigarette smoked  
238 per day).<sup>41</sup> Our literature review found that alcohol use is also an important modifiable risk factor, as  
239 high alcohol consumption during the first trimester is associated with an increase in miscarriage risk  
240 (aOR 1.67; 95% CI 1.31-2.19; Table 6).<sup>25,39,62-70</sup> Our review indicated that high caffeine intake might  
241 be associated with miscarriage (aOR 1.56; 95% CI 0.98-2.50; Table 6), although there was statistical  
242 uncertainty in the finding.<sup>25,39,71</sup> Furthermore, any association between caffeine and miscarriage is  
243 likely to be confounded by the fact that a healthy pregnancy is associated with nausea and vomiting  
244 (due to pregnancy hormones), which in turn may reduce caffeine consumption.<sup>72</sup> Our literature  
245 searches found that night shift work is associated with an increased risk of miscarriage (aOR 1.43;  
246 95% CI 1.25-1.71; Table 6). This risk appeared to follow a dose-response relationship. Our review of  
247 the evidence also found that high stress is associated with miscarriage risk (aOR 1.46; 95% CI 1.16-  
248 1.77; Table 6)<sup>66,71,73-77</sup>; however, there is no evidence that the association represents a causal link  
249 because, for example, preconception stress, as measured by basal salivary cortisol and alpha-  
250 amylase concentrations, did not predict subsequent pregnancy loss.<sup>78</sup>

251

252 *Clinical risk factors*

253 An important determinant of risk of miscarriage is the gestational age of a pregnancy. The risk of  
254 pregnancy loss decreases with advancing gestational age.<sup>79-82</sup> Once the pregnancy reaches 8 weeks,  
255 the risk of miscarriage decreases significantly; conversely, the likelihood of having a successful live  
256 birth approaches 97-98%.<sup>82</sup>

257 The number of previous miscarriages is a major determinant of miscarriage risk; the relationship is  
258 consistent across various studies, and demonstrates a biological gradient according to the number of  
259 previous miscarriages.<sup>83</sup> Several maternal conditions, including antiphospholipid antibodies, thyroid

260 autoantibodies and subclinical hypothyroidism, are associated with miscarriage (Table 6). Uterine  
261 anomalies, in particular canalization defects such as uterine septae, have been associated with both  
262 spontaneous and recurrent miscarriage.<sup>84</sup>

263 Bacterial (bacterial vaginosis, brucellosis, chlamydia trachomatis, and syphilis), viral (herpes virus:  
264 HSV-1 and HSV-2, human CMV, human papillomavirus, parvovirus, adeno-associated viruses,  
265 parvovirus B19, bocavirus, HIV, polyomavirus, Dengue fever, hepatitis B, hepatitis C, rubella,  
266 coronaviruses [SARS, MERS and H1N1]) and protozoa (malaria and toxoplasmosis) infections have all  
267 been linked to miscarriage.<sup>85</sup> In the era of bacterial community assessment using DNA sequencing,  
268 there is evolving evidence linking the composition of the vaginal microbiome to miscarriage.<sup>86</sup>

269 Miscarriage is more commonly associated with a lactobacillus deplete microbiota, but whether this  
270 is cause or effect, or what the potential mechanisms are remains unclear. These findings are  
271 supported by older data using more traditional microbiology techniques which showed an increase  
272 in the risks of miscarriage in women with bacterial vaginosis.<sup>87</sup> Sperm DNA fragmentation is  
273 associated with miscarriage (Table 6).<sup>88</sup> Association between sperm DNA fragmentation and  
274 smoking, recreational drugs, and obesity, as well as treatment with lifestyle changes and anti-  
275 oxidants are important research questions.

276

### 277 *Environmental risk factors*

278 Air pollution, composed of both primary pollutants, those emitted directly from the source, and  
279 secondary air pollutants formed from the interaction of primary pollutants within the atmosphere,  
280 has a wide impact on human health. In the context of pregnancy air pollution is linked to stillbirth,  
281 preterm delivery and low birthweight.<sup>89,90</sup> A large study assessed the effect of exposure to air  
282 pollution on miscarriage rates in Beijing, demonstrating a strong relationship with miscarriage (OR  
283 1.51; 95% CI 1.33-1.69).<sup>91</sup> Similarly, a case-control study on women attending an emergency  
284 department in Utah<sup>92</sup> found that a 10 parts-per-billion rise in nitrogen oxide levels was associated  
285 with an increased risk of miscarriage (OR 1.16; 95% CI 1.01-1.33). The Nurses' Health Study II showed

286 a positive association between particulate air pollution and miscarriage.<sup>93</sup> Exposure to air pollution  
287 therefore appears to increase miscarriage risk and constitutes a modifiable risk factor (Table 6).  
288 Pesticides have been linked to recurrent miscarriage (Table 6). Exposure to sprayed pesticides in  
289 rural South Africa in the first three months of pregnancy was associated with an increased risk of  
290 miscarriage (OR 2.8; 95% CI 1.1-7.2).<sup>94</sup> This epidemiological study correlates with a clinical study  
291 demonstrating higher levels of serum organochlorine pesticides in women with recurrent  
292 miscarriage compared with controls.<sup>95</sup>

293

## 294 **Risks and complications of miscarriage**

### 295 *Threatened miscarriage and obstetric complications*

296 Threatened miscarriage, defined as vaginal bleeding in early pregnancy, is among the most common  
297 reasons for women to seek medical care in early pregnancy.<sup>96</sup> It is increasingly clear that events in  
298 early pregnancy have a significant impact on pregnancy outcomes.<sup>97-100</sup> A systematic review of 14  
299 studies (n=64,365) found that women who experienced threatened miscarriage have a higher risk of  
300 antepartum haemorrhage due to placenta previa (OR 1.62; 95% CI 1.19-2.22) or antepartum  
301 haemorrhage of unknown origin (OR 2.47; 95% CI 1.52-4.02).<sup>97</sup> There is also an association with  
302 preterm prelabour rupture of membranes (OR 1.78; 95% CI 1.28-2.48), preterm delivery (OR 2.05;  
303 95% CI 1.76-2.40), and fetal growth restriction (OR 1.54; 95% CI 1.18-2.00).<sup>97</sup> Significantly higher  
304 rates of perinatal mortality (OR 2.15; 95% CI 1.41-3.27) and low-birthweight neonates (OR 1.83; 95%  
305 CI 1.48-2.28) have been reported.<sup>97</sup> Ultrasound diagnosis of intrauterine haematoma (IUH) is also  
306 associated with an increased risk of antenatal complications such as preeclampsia (Relative Risk [RR]  
307 4.0; 95% CI 2.4-6.7), placental abruption (RR 5.6; 95% CI 2.8-11.1) and preterm delivery (RR 2.3; 95%  
308 CI 1.6-3.2).<sup>99</sup>

309

310

311

312 *Miscarriage and obstetric complications*

313 Our literature review demonstrated striking associations between a history of miscarriage and  
314 several adverse obstetric outcomes in subsequent pregnancies (Table 7). The risk of preterm birth  
315 increases stepwise with each previous miscarriage, demonstrating a biological gradient; this  
316 association persists even with adjustment for confounding variables (Table 7). It is possible that  
317 adverse outcomes after miscarriage may be at least partly attributable to the management of  
318 miscarriage. Repeated uterine curettage after cervical dilatation may cause injury to the uterine  
319 cervix and endometrial cavity or change the uterine microbiome, increasing the risk of preterm birth  
320 due to cervical insufficiency or chronic endometritis. Injury to the uterine wall or endometrium may  
321 also cause abnormal placentation in subsequent pregnancies, resulting in increased risk of placental  
322 abruption and placenta praevia (Table 7). A nationwide population-based birth cohort study in Japan  
323 found an increased risk of placental adhesions and uterine infection in women with recurrent  
324 pregnancy loss.<sup>101</sup> Abnormal placentation may also contribute to low birthweight (Table 7).  
325 However, it is plausible that the increased frequency of low birthweight and perinatal complications  
326 is an inherent part of the recurrent miscarriage syndrome. Women who experience recurrent  
327 miscarriage are themselves born with a significantly reduced birthweight,<sup>102</sup> and a history of  
328 perinatal complications has been found in women in their pregnancies before they acquire a  
329 recurrent miscarriage diagnosis.<sup>103</sup> An inadequate decidual response, if it does not lead to  
330 miscarriage, may lead to inadequate placentation causing placental dysfunction disorders, and so  
331 increasing the risk of, placental abruption, fetal growth restriction, preterm birth and perinatal  
332 death. There is growing evidence that preterm infants born after spontaneous preterm labour have  
333 a lower mean birthweight than what would be expected for their gestation.<sup>104-106</sup> Therefore, the  
334 likelihood is that the association between miscarriage and adverse obstetric outcomes may partly be  
335 driven by a common aetiology, perhaps originating in suboptimal endometrial repair and  
336 decidualisation. The increasing incidence of perinatal complications with increasing number of  
337 previous pregnancy losses<sup>107</sup> suggests a need for heightened antenatal surveillance in patients with a

338 history of multiple miscarriages. In addition, miscarriage is an opportunity to consider prophylactic  
 339 interventions, such as lifestyle improvements before another pregnancy.

340

341 **Table 7.** Risks and complications associated with past history of miscarriage

	Crude estimates		Adjusted estimates	
	Number of participants (trials)	Odds ratio [95% CI]	Number of participants (trials)	Odds ratio [95% CI]
<b>Maternal risks</b>				
<b>Pre-eclampsia or pregnancy induced hypertension</b>				
1 miscarriage	719,644 (4)	1.02 [0.98, 1.06]	697,122 (3)	0.99 [0.95, 1.03]
2 miscarriages	622,504 (2)	1.03 [0.95, 1.12]	622,504 (2)	0.94 [0.85, 1.04]
3 or more miscarriages	671,060 (5)	1.04 [0.72, 1.51]	616,146 (3)	1.22 [0.86, 1.73]
<b>Placental abruption</b>				
1 miscarriage	719,644 (4)	1.09 [0.98, 1.21]	697,122 (3)	1.07 [0.95, 1.20]
2 miscarriages	74,925 (2)	1.33 [1.07, 1.66]	622,504 (2)	1.26 [1.00, 1.59]
3 or more miscarriages	646,199 (4)	1.70 [1.31, 2.19]	616,146 (3)	1.67 [1.21, 2.30]
<b>Placenta praevia</b>				
1 miscarriage	115,290 (3)	1.41 [1.17, 1.69]	92,768 (2)	1.40 [1.15, 1.70]
2 miscarriages	74,925 (2)	1.86 [1.34, 2.57]	74,925 (1)	1.86 [1.34, 2.58]
3 or more miscarriages	106,207 (3)	2.71 [1.54, 4.76]	76,154 (2)	2.81 [0.87, 9.04]
<b>Neonatal risks</b>				
<b>Preterm birth</b>				
1 miscarriage	875,911 (7)	1.24 [1.09, 1.41]	733,199* (7)	1.17 [1.05, 1.31]
2 miscarriages	767,888 (4)	1.40 [1.10, 1.80]	675,655** (5)	1.36 [1.13, 1.63]
3 or more miscarriages	1,451,303 (9)	2.23 [1.68, 2.97]	668,615** (6)	1.76 [1.39, 2.22]
<b>Low birthweight <math>\diamond</math></b>				
1 miscarriage	115,182 (3)	1.11 [0.88, 1.40]	115,182* (3)	1.09 [0.91, 1.30]
2 miscarriages	74,829 (1)	1.08 [0.96, 1.21]	74,829* (1)	1.37 [0.81, 2.32]
3 or more miscarriages	76,614 (3)	1.87 [1.07, 3.27]	76,061* (3)	1.98 [1.09, 3.58]
<b>Stillbirth</b>				
1 miscarriage	715,168 (3)	1.13 [0.96, 1.33]	715,168 (3)	1.00 [0.88, 1.13]
2 miscarriages	623,133 (2)	1.08 [0.83, 1.41]	623,133 (2)	1.04 [0.79, 1.38]
3 or more miscarriages	613,013 (2)	2.01 [1.43, 2.82]	613,013 (2)	1.69 [1.17, 2.45]
<b>Health risks</b>				
<b>Cardiovascular complications</b>				
1 miscarriage	2,431,899 (6)	1.18 [0.83, 1.68]	2,450,098 (6)	1.06 [0.98, 1.15]
2 miscarriages	50,605 (2)	1.58 [0.64, 3.89]	162,259 (5)	1.22 [1.10, 1.35]
3 or more miscarriages	176,081 (4)	5.04 [1.68, 15.14]	290,188 (7)	1.42 [1.16, 1.74]
<b>Stroke</b>				
1 miscarriage	2,430,267 (4)	1.05 [0.65, 1.72]	2,448,174 (5)	0.98 [0.91, 1.06]
2 miscarriages	2,250,752 (4)	1.00 [0.38, 2.61]	86,319 (3)	1.10 [0.99, 1.21]
3 or more miscarriages	59,735 (3)	1.52 [0.70, 3.30]	17,645 (1)	1.15 [0.98, 1.36]
<b>Venous thromboembolism</b>				
1 miscarriage	94,595 (1)	1.30 [0.73, 2.32]	94,595 (1)	1.11 [0.59, 2.06]

2 miscarriages	80,792 (1)	1.57 [0.57, 4.36]	-	-
3 or more miscarriages	78,020 (3)	10.91 [5.16, 23.06]	78,020 (3)	6.13 [2.48, 15.16]
<b>Mental health risks</b>				
<b>Anxiety</b>				
1 miscarriage	3,028 (3)	1.74 [1.11, 2.73]	3,889 (4)	1.62 [1.25, 2.11]
2 or more miscarriages	146 (1)	4.34 [2.08, 9.03]	-	-
<b>Depression</b>				
1 miscarriage	4,179 (6)	2.79 [1.56, 5.01]	4,095 (5)	2.38 [1.65, 3.42]
2 or more miscarriages	146 (1)	3.88 [1.87, 8.03]	-	-
<b>Post traumatic stress disorder</b>				
1 miscarriage	1,513 (2)	4.39 [0.18, 105.50]	-	-
2 or more miscarriages	146 (1)	4.89 [1.57, 15.27]	-	-
<b>Suicide</b>				
1 miscarriage	3,655 (1)	5.27 [4.12, 6.74]	3,655 (1)	3.80 [2.80, 5.20]

342 The reference group for all comparisons is women without previous miscarriages. \* Number of women missing  
 343 for one study; \*\* Number of women missing for two studies; ◊ Excluding growth restriction.  
 344

#### 345 *Miscarriage and long-term health risks*

346 Recurrent miscarriage is associated with long term health problems beyond pregnancy. Our  
 347 literature review found that recurrent miscarriage is associated with cardiovascular disease and  
 348 venous thromboembolism (Table 7). No association was identified between miscarriage and stroke  
 349 (Table 7). These findings are important because they add to the concept of a recurrent miscarriage  
 350 syndrome, and may mean that a history of repeated miscarriage is an opportunity for reducing risks  
 351 for cardiovascular and thromboembolic disease.

352 The psychological consequences of miscarriage involve both trauma and bereavement.<sup>108</sup> The  
 353 psychological consequences of miscarriage may have little or no outward physical manifestation and  
 354 so can go unrecognised by healthcare professionals, family and friends. This is the case particularly in  
 355 a society which views miscarriage as unimportant or shameful, thus leading to concealment of a  
 356 pregnancy loss and its consequences.

357 Our literature review identified that anxiety (aOR 1.62; 95% CI 1.25-2.11), depression (aOR 2.38; 95%  
 358 CI 1.65-3.42) and suicide (aOR 3.80; 95% CI 2.8-5.2) are strongly associated with miscarriage (Table  
 359 7). A multicentre prospective cohort study of 537 women following a miscarriage found that nine  
 360 months after a pregnancy loss, 18% of women met the criteria for post-traumatic stress, 17% for

361 moderate or severe anxiety, and 6% for moderate or severe depression.<sup>109</sup> Identifying women at risk  
362 of psychological distress following miscarriage and the development of optimal treatment strategies  
363 have been identified as research priorities.<sup>110</sup>

364

### 365 **Economic burden**

366 We conducted a literature review with the goal of identifying and summarising evidence on the  
367 economic costs associated with miscarriage, the cost-effectiveness of prevention or management  
368 strategies, and preference-based outcomes associated with miscarriage or its prevention or  
369 management derived using economic methods. A total of 30 articles were included; 15 articles  
370 reported costing studies, 12 articles reported economic evaluations, and 3 articles reported  
371 preference elicitation studies. Due to heterogeneity in study design, outcomes and intervention  
372 types, and variations in healthcare practices and relative prices for resource inputs, a narrative  
373 synthesis of economic evidence is presented. All economic costs are presented in Pounds Sterling  
374 (2018 prices) for comparative purposes.

375 Published evidence on the economic consequences of miscarriage has focussed largely on direct  
376 health service costs associated with miscarriage treatment procedures. Cost estimates vary by the  
377 nature of the intervention (e.g. expectant, medical or surgical management), location of care  
378 (inpatient or outpatient), cost accounting methodology and jurisdiction. Most published studies have  
379 aimed to provide information about options that are less costly than current practice,<sup>111-118</sup> or to  
380 probe the value of adjuncts to current practice.<sup>119</sup> The emphasis is usually on cost comparisons for  
381 achieving a standard outcome, namely complete removal of pregnancy tissue from the uterus. The  
382 use of decision analysis is common,<sup>111,118</sup> mainly as a means of tracking cumulative costs over  
383 different treatment pathways particularly where additional treatment may be required following  
384 failure of initial therapy. Unit costs estimates have been derived from a number of sources, including  
385 primary research methods<sup>113,115,116</sup> and administrative tariffs.<sup>120,121</sup>

386 Published estimates of direct health service costs associated with miscarriage treatment procedures  
387 vary considerably between and within countries. However, a consistent pattern emerges with direct  
388 health service costs highest for surgical management and generally lowest for expectant  
389 management. Direct health service costs for expectant management ranged from £380 in a study  
390 from the United States<sup>120</sup> through to £1067 in a study from Hong Kong.<sup>118</sup> Direct health service costs  
391 for medical management ranged from £298 in a study from the United States<sup>120</sup> through to £1421 in  
392 a UK study.<sup>113</sup> Direct health service costs for surgical management, usually curettage, ranged from  
393 £455 in a study from Finland<sup>122</sup> through to £2242 in a study from Spain.<sup>111</sup> In a comparison of  
394 outpatient versus inpatient treatment in the United States, the cost of manual vacuum aspiration as  
395 an outpatient (£852) was much lower than that for inpatient treatment (£1729).<sup>121</sup> Direct health  
396 service costs associated with evacuation procedures are generally lower in low income countries. For  
397 example, in Pakistan manual vacuum aspiration was estimated to cost on average £56,<sup>123</sup> curettage  
398 £146<sup>123</sup> and electrical vacuum aspiration £193,<sup>115,116</sup>; in Swaziland manual vacuum aspiration was  
399 estimated to cost on average £131 and dilation and curettage £201 for incomplete first trimester  
400 miscarriages.<sup>124</sup> Estimates of direct health service costs not differentiated by treatment method  
401 ranged from £401 in the Netherlands (care provided in an early pregnancy assessment unit)<sup>117</sup> to  
402 £973 in the UK (progesterone as a preventive therapy).<sup>119</sup>

403 A few studies have estimated the non-health care costs associated with miscarriage or its  
404 management. Where these have been estimated, the focus has largely been on the economic value  
405 of lost productivity for women experiencing miscarriage. As part of the economic evaluation  
406 conducted alongside the MIST trial, the investigators asked study participants to estimate time taken  
407 off work as a consequence of their miscarriage at 10-14 days and 8 weeks following trial entry.<sup>113</sup>  
408 The mean value of work absences was estimated at £431 with no significant difference in values  
409 observed between the three management methods evaluated (expectant, management, surgical). In  
410 a study in the Netherlands, the estimated value of lost productivity was ostensibly similar (£439), but  
411 its composition notably different, with most of it driven by lower productivity after women had



412 returned to work rather than time off work.<sup>125</sup> A broadly similar estimate of £428-£521 (depending  
413 on the treatment strategy) emerges in another economic evaluation from the Netherlands<sup>126</sup> that  
414 compared misoprostol treatment and curettage in women who had been managed expectantly for  
415 at least one week. Amongst women allocated to the misoprostol arm, the mean value of lost  
416 productivity exceeded mean direct costs to the health care system.

417 The economic studies emerging from our literature review typically adopt a short-term time horizon,  
418 focusing on the initial treatment period. They do not cover long lasting effects such as the economic  
419 consequences associated with increased risk of psychological morbidity.

420 Evidence generated by the literature review can act as data inputs into burden of illness calculations.

421 For example, assuming that the economic consequences of miscarriage are felt only over the short  
422 term and combining national prevalence data for England with estimates of costs of hospital and  
423 community health and social services,<sup>113</sup> costs to patients<sup>127</sup> and broader societal costs associated  
424 with lost productivity<sup>113</sup> generates an annual national estimate of economic burden of £471 million.

425 Economic estimates such as these can contribute to clinical and budgetary service planning.

426

## 427 **Discussion**

428 Miscarriage is common, but its scale and impact are not fully appreciated by women, family, care  
429 providers, policy makers and healthcare funders. There are multiple risk factors for miscarriage,  
430 most prominently female age and the number of previous losses. Certain risk factors are modifiable,  
431 for example, BMI, smoking and alcohol. Environmental risk factors are an emerging concern.

432 However, it is important to appreciate that an association does not imply causation, and there is a  
433 need to better understand the nature, mechanisms and implications of many of the associations  
434 highlighted in this article. The physical consequences of miscarriage are well appreciated, but  
435 psychological sequelae less so. Even less well appreciated are future reproductive, obstetric and  
436 health consequences, particularly the risk of miscarriage recurrence, preterm birth and placental

437 disorders in future ongoing pregnancies, and cardiovascular disease and venous thromboembolism  
438 later in life.

439 Whilst there are data on the short-term costs of miscarriage, the long-term costs might be  
440 considerable and may outweigh short-term concerns, although the data are limited. Newly emerging  
441 cohort studies with long term follow-up, such as the Tommy's Net Cohort Study,<sup>128</sup> and population-  
442 wide record linkage studies provide potential vehicles for ascertaining long-term economic  
443 outcomes such as downstream use of health and social care services, employment and occupational  
444 status, income, receipt of social welfare benefits and reproductive health, which might in turn have  
445 economic sequelae. Future research should use evidence from economic evaluations encompassing  
446 information on incremental costs and incremental health gains associated with prevention and  
447 treatment strategies to inform decisions around the prioritisation of health care resources in this  
448 area.

449 We recommend miscarriage data are gathered and reported to facilitate comparison of miscarriages  
450 rates amongst countries, to accelerate research, and to improve patient care and policy  
451 development. Key epidemiological research priorities include determining how can we monitor  
452 miscarriage rates on a population basis; ascertaining if miscarriage risk and prevalence differs across  
453 nations and ethnic groups, whether miscarriage rate are increasing, and if so why; what are the key  
454 outcomes from women's point of view; and which risk factors for miscarriage are potentially  
455 causative, modifiable, and the impact of modification of the risk factor on clinical outcomes.

456 Important clinical research questions include the role of sperm DNA damage on miscarriage, both  
457 diagnosis and the treatment; development of effective screening instruments to detect women  
458 suffering from severe stress disorders and anxiety as a consequence of miscarriage, and the  
459 evaluation of therapies to treat these disorders; and a better understanding of the impact of air  
460 pollution on miscarriage. Concerted effort from both researchers and national policy makers is  
461 needed to address these issues.

462 The current evidence indicates that smoking cessation and stress management should be prioritised  
463 to improve general health and reduce the risk of miscarriage. Alcohol should be avoided in early  
464 pregnancy, fruit and vegetables should be thoroughly washed to avoid the risk of ingesting  
465 pesticides, and the possibility of reducing night shifts should be explored. Women with a history of  
466 miscarriage, particularly those with three or more miscarriages, are at an increased risk of obstetric  
467 complications including pre-term birth. Therefore, these women should be treated as high risk  
468 patients during antenatal and intrapartum care. We recommend that robust strategies are  
469 developed, evaluated and scaled up to manage these risks associated with miscarriage, particularly  
470 psychological morbidity and future obstetric consequences.

471

#### 472 **Contributors**

473 All authors participated in the design of the review, literature searches, and assisted with the writing  
474 a review of all sections and agreed to submit the manuscript. The manuscript represents the view of  
475 named authors only.

476

#### 477 **Declaration of interests**

478 The authors have no conflicts of interest to declare.

479

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485

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