

Causes of maternal death in Ethiopia between 1990 and 2016: systematic review with meta-analysis

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Abstract

Background: Even though Ethiopia has achieved the Millennium Development Goal targets for child health set for 2015 by the international community, it has failed to do so with regard to maternal health. Maternal deaths are still high, with an estimated maternal mortality ratio of 412 maternal deaths per 100,000 live births in 2016. The causes of maternal death and individual, environmental and health systems related gaps contributing to maternal death in Ethiopia remain unclear.

Objectives: The main aim of this study was to document the causes of maternal deaths and risk factors contributing to deaths aggravated by pregnancy and its management in Ethiopia over the period 1990 to 2016, using a systematic review with meta-analysis.

Methods: Manuscripts were reviewed on causes of maternal death that were published in scientific journals and grey literature, including the compendium of abstracts presented in the series of annual conferences of the Ethiopian Public Health Association, masters' theses in public health from different public universities in Ethiopia, and periodic reports of the Federal Ministry of Health of Ethiopia. A comprehensive and reproducible literature search was used, employing the Cochrane systematic literature review technique. Medical subject heading terms – including maternal deaths, maternal mortality, causes of maternal mortality/death, maternal mortality/death in Ethiopia and etiology of maternal mortality/death in Ethiopia – were used to search the required articles. A total of 146 articles (134 from online sources and 12 hard copies) were identified on the basis of their titles and abstracts. Of these, 24 were found to be suitable for further analysis by applying the review criteria, which were then synthesized to identify the main causes of maternal death, as well as the risk factors affecting the patterns of deaths.

Results: The main direct causes of maternal death in Ethiopia include obstetric complications such as hemorrhage (29.9%; 95% CI: 20.28%-39.56%), obstructed labor/ruptured uterus (22.34%; 95% CI: 15.26%-29.42%), pregnancy-induced hypertension (16.9%; 95% CI: 11.2%-22.6%), puerperal sepsis (14.68%; 95% CI: 10.56%-18.8%), and unsafe abortion (8.6%; 95% CI: 5.0%-12.18%). In recent years, hemorrhage has been the leading cause of mortality, followed by hypertensive disorders of pregnancy and sepsis, while the contributions of obstructed labor and abortion have decreased over the period. The most reported indirect causes of maternal death were anemia (10.39%; 95% CI: 4.79%-15.98%) and malaria (3.55%; 95% CI: 1.50%-3.30%).

Conclusions: The nationwide registration of causes of maternal death should be strengthened to understand the causes in detail, their attributes, as well as the patterns of causes of death. The health sector should sustain its current effort to tackle the diverse causes of maternal death in Ethiopia. [*Ethiop. J. Health Dev.* 2018;32(4):225-242]

Key words: maternal mortality, systematic review, causes of maternal death, Ethiopia

Background

Maternal death refers to the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes (1).

The causes of maternal death are generally classified as direct or indirect. Direct causes result from obstetric complications due to interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above, and include hemorrhage, obstructed labor, pregnancy-induced hypertension, puerperal sepsis, and unsafe abortion. Indirect causes are deaths that result from previously existing diseases, or diseases that developed during pregnancy, that are aggravated by the physiological effects of pregnancy (2).

With one of the highest maternal mortality ratios in Sub-Saharan Africa, Ethiopia has failed to achieve its maternal health Millennium Development Goals (MDGs). According to the 2016 Ethiopian Demographic Health Survey (EDHS), maternal mortality ratio was estimated to be 412 per 100,000 live births. Maternal death accounts for around a quarter of all deaths in women aged 15-49 (3). Although there are variations in the estimated magnitude of maternal death, it has continued to be the main MDG-related challenge that Ethiopia has failed to overcome (4).

One target set under the Sustainable Development Goal (SDG3) is to reduce the global maternal mortality ratio to less than 70 per 100,000 births, with no country having a maternal mortality ratio of more than twice the global average (5). The World Health Organization recommends registration of maternal deaths and its causes both from facilities, administrative sources and

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surveys as crucial to get better information for better action (6). We therefore need to document the main causes of maternal death and gaps which have been contributing to these causes of death in the past decade and a half, before embarking on interventions to achieve the SDG target.

The Federal Ministry of Health of Ethiopia launched the national maternal death surveillance and response (MDSR) system in May 2013 as a tool to improve the quality of maternal health care, particularly during pregnancy, childbirth and the postpartum periods. In addition, the Vital Events Registration Agency (VERA) started the registration of vital events, including causes of death, in August 2016. Moreover, the Ethiopian government has re-affirmed its commitment in reducing MMR from 420 to 199 per 100,000 live births by 2020 (7).

As the documentation of the causes of maternal death enhances the delivery of focused interventions to avert deaths resulting from preventable causes, the proper registry of events should be accorded the utmost attention to ensure attainment of the envisaged SDG in the stipulated time. In terms of such efforts, Abdella conducted a systematic review of the trends and causes of maternal mortality in Ethiopia from 1970 to 2008 (8). Similarly, Berhan *et al.* conducted a literature review of trends in MMR from 1977 to 2012 (4), and also documented the trends of the direct causes from 1980 and 2012 on the basis of published articles (9).

The present review evaluated both direct and indirect causes of maternal deaths in Ethiopia using both published and grey literature from 1990 to 2016, and identified maternal death risk factors that are aggravated by pregnancy and its management in Ethiopia. It provides the most up-to-date study of the causes of maternal deaths with its pooled effects, and the lessons identified can help strengthen the documentation efforts for facilitating the delivery of focused interventions to mitigate the problems of maternal mortality in the country.

Methods

Published and grey literature on the causes of maternal deaths in Ethiopia during the period 1990 to 2016 were reviewed. Moreover, literature on individual behavior, environmental and health system related gaps contributing to maternal death during the specified

period were also consulted. The Cochrane systematic literature review technique was utilized.

As a criterion to identify the causes of maternal death, descriptive, analytical and experimental studies were included in the review. Literature which defines maternal death according to the WHO disease classification code version 9 or 10, using 24 directly observed or measured causes of maternal death and three studies on gaps contributing to death were included in the review. Qualitative studies, systematic reviews, commentaries, model outputs and opinion articles were, however, excluded from the review.

Sources for literature review: We searched the electronic databases of Pub Med, Medline, Google Scholar and Embase in order to identify the causes of maternal deaths in Ethiopia between 1990 and 2016. In addition, grey literature was included from academic staff projects, graduate students' theses and dissertations, as well as abstract compendiums of annual conference proceedings of the Ethiopian Public Health Association and other medical and nursing associations in Ethiopia. To ensure literature saturation, the reference lists of included published studies or relevant reviews identified through the search were also scanned. Authors were contacted in cases of incomplete information from a certain manuscript or report. Selected articles were shared with members of the systematic review research team to validate their importance using a set of criteria to abstract valuable information.

Medical subject heading (MeSH) terms –including maternal deaths, maternal mortality, causes of maternal mortality/death, maternal mortality/death in Ethiopia and etiology of maternal mortality/death in Ethiopia– were used as the basis of the bibliographic search. Two reviewers conducted the search during November and December 2016, and verification of the search process was made during a retreat workshop by the team of stakeholders, pooled from governmental and non-governmental offices working on maternal and child health in Ethiopia, to minimize the possibility of missing potential literature.

Study selection: A total of 146 references were retrieved from electronic databases and manual searches. After removing duplicates and abstracts which did not include the search terms, 24 studies were included in this systematic review (Figure 1).

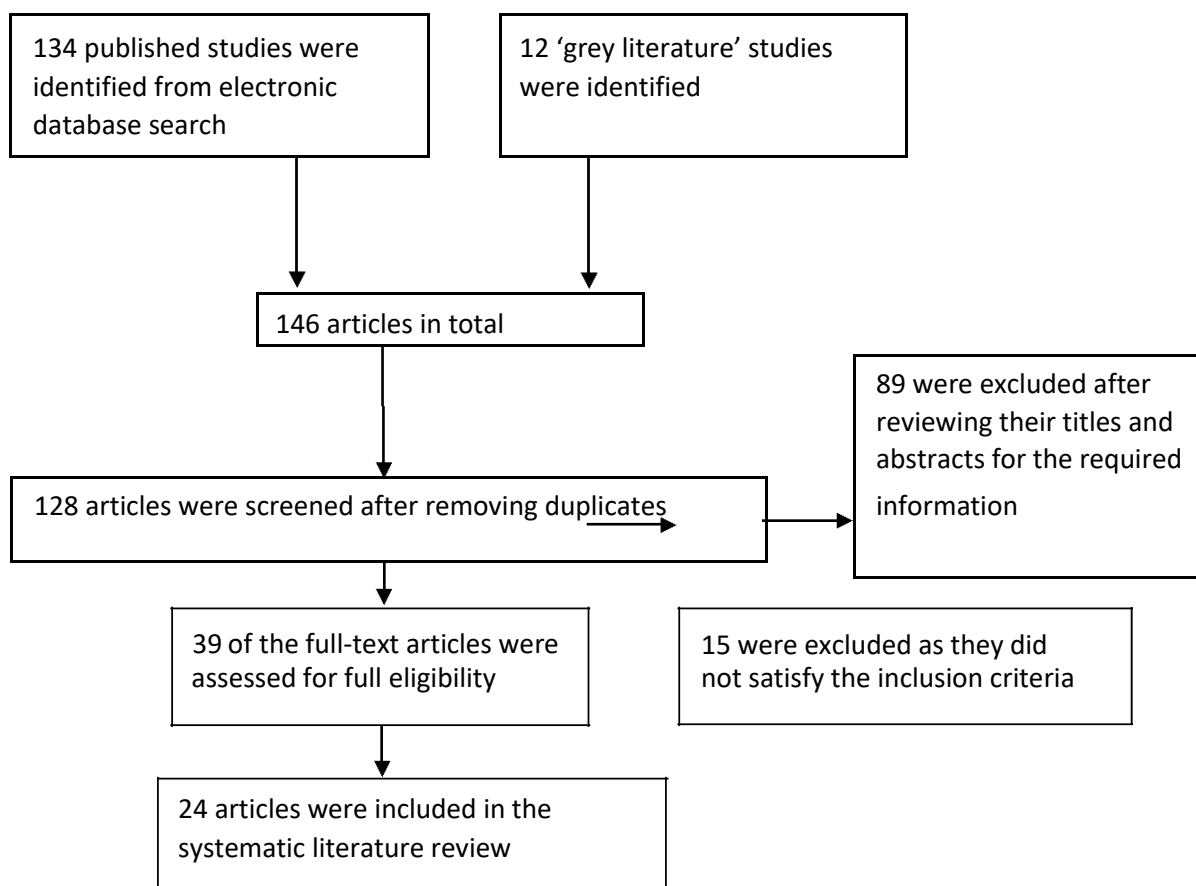


Figure 1: Flow chart showing systematic selection of literature in the review

Data extraction: An abstraction form was developed to retrieve relevant information from the eligible documents. The data extraction form included authors' name, year of publication, study objective, place, design and population, sample size and procedure, data collection procedures, effect measures of predictors of maternal death and analysis procedures, causes of maternal death, and critics of the method. The data abstraction form was completed by two research team members and was re-checked by a group of researchers, pooled from different organizations working on maternal and child health in Ethiopia, to ensure the quality of abstracted information.

Quality assessment: The quality of the reviewed literature was assessed using the Newcastle–Ottawa Scale for assessing the quality of non-randomized studies in meta-analysis (10). The assessment criteria included study participant selection, comparability of study groups, and methods for outcome or exposure ascertainment, and adequacy of follow-up. It contained

separate criteria for cross-sectional, case-control, and cohort studies: cohort and case-control studies were given maximum scores of 4, 2, and 3 on the selection, comparability and outcome/exposure criteria, respectively; while cross-sectional studies are awarded a maximum of 4, 2, and 2 scores for the selection, comparability and outcome criteria, respectively. The overall quality assessment was classified as 'high' (≥ 6 score), 'medium' (4-5 score), or 'low' (≤ 3 score). No reviewed literature was excluded because of its poor performance in the quality assessment; rather, the methodological rigor of the studies was detailed.

It should be noted that most of the reviewed studies were conducted in health facility settings, which might limit their generalizability to the general Ethiopian population. On the other hand, the quality appraisal using the Newcastle–Ottawa Scale indicated that 11 of the included studies are high quality, with 10 assessed as having medium quality, and three as low quality, respectively (Table 1).

Table 1: **Quality assessment of reviewed literature**

Authors	Study design	Selection	Comparability	Outcome/ Exposure	Total score
Worku <i>et al.</i> , 2013	Prospective Cohort study	***		**	
Girma <i>et al.</i> , 2013	Retrospective chart review	**		**	
Yaya <i>et al.</i> , 2014	Cross-sectional study	**	*	*	
Yaya <i>et al.</i> , 2015	Registering maternal deaths	**	*	*	
Gebrehiwot Tewolde, 2014	an Cross-sectional study	**		**	
Godefay <i>et al.</i> , 2015	Case-control study	***		*	
Berhan & Endeshaw, 2015	Retrospective cohort study	**		**	
Kelly <i>et al.</i> , 2010	Retrospective cohort study	***		*	
Legese <i>et al.</i> , 2016	Case-control study	*		***	
EPHI, 2016	National MDSR	**		**	
Chufamo <i>et al.</i> , 2015	Prospective cohort study	***		*	
Godefay <i>et al.</i> , 2015	Cross-sectional study	**		*	
Tesfaye, 2015	Cross-sectional study	*		**	
Gessesew & Barnabas, 2009	Retrospective chart review	*		**	
Ali, 1994	Cross-sectional study	*		*	
Gaym, 2000	Retrospective chart review			**	
Hailu <i>et al.</i> , 2009	Cross-sectional study			**	
Negussie & Mesfin, 2009	Retrospective chart review	*		*	
Deneke <i>et al.</i> , 2014	Retrospective registry review			**	
Kassie <i>et al.</i> , 2014	Cross-sectional study			**	
Wolde <i>et al.</i> , 2011	Cross-sectional study			**	
Prata <i>et al.</i> , 2012	Vital registration	*		—	
Gessesew & Melese, 2002	Retrospective chart review			*	
Assefa, 2016	HDSS	**		—	

HDSSs = health and demographic surveillance systems

Data analysis and synthesis: The main characteristics of studies included in the review (causes and individual behavior, environmental and health system related gaps contributing to maternal death in Ethiopia from 1990 to 2016) are presented in summarized narration with meta-analysis. Specifically, there were only a few studies that documented indirect causes of maternal death. The focus of classification was mainly on the major causes of maternal deaths, which were documented in several eligible articles and categorized into seven groups: hemorrhage, sepsis and other pregnancy-related infections, hypertensive disorders of pregnancy (HDP), obstructed labor, abortion, other direct causes of maternal disorders in the direct causes of maternal death, and indirect causes in one group.

The review tried to show the patterns of direct and indirect causes of maternal death by looking at the magnitude of each of the causes and date of report of the study. We have ordered the studies included in the

review according to their date of report of the event for each of the causes. Then we ranked each of the causes according to the magnitude they have in each of the studies. The rank is presented in number form, i.e. 1 being the leading cause of maternal death compared with other causes described in the study.

Moreover, in order to compute the pooled magnitude of major direct and indirect causes of maternal death, data were entered into Microsoft Excel and then exported to STATA version 13 software for further analysis. The effect size of the meta-analysis was attributed to the main direct and indirect causes of maternal death. Due to observed heterogeneity, the pooled effect was estimated using the random effects model. A forest plot was used to present the combined estimates with their 95% confidence interval (CI). Subgroup analysis was conducted by years of the maternal deaths recorded. The findings of the review and meta-analysis were

presented using a table and the forest plots. A p-value of less than 0.05 was used to declare heterogeneity.

Results

Overview of reviewed literature: A total of 146 references were retrieved through electronic and manual searches. After removing duplicates found using different search engines, 89 of the articles/reports were excluded by assessing the title/abstract alone, and 15 more articles/reports were dropped following the full-text review (Figure 1). Finally, only 24 articles/reports were included in the systematic literature review (1, 11-33). Three of these (20, 31, 33) were articles/reports of national studies, while the remaining 21 were carried out in specific regions or small communities in Ethiopia. Moreover, there were variations in the settings where the studies were conducted. Sixteen of the reviewed articles were health

facility-based studies (1, 11-17, 19, 21, 22, 24, 25, 29, 32, 33), conducted indifferent referral, regional or district hospitals and health centers; the remaining eight were community-based studies (18,20,23,26-28,30,31). With regard to the study design, eight were cross-sectional studies (1, 18, 19, 24, 25, 28, 32, 33), six retrospective chart reviews(13-17,22), two case-control studies (29, 30), two retrospective cohort studies (11,21), two prospective cohort studies (12, 26), three were hosted by health and demographic surveillance systems (HDSSs) (23, 27, 31) which employed longitudinal research design, and one was maternal death surveillance and response (MDSR) system reports (20). The characteristics of the 24 studies included in the review are described in detail in Table 2.

Table 2: Summarized description of literature included in the systematic literature review

Authors	Year of report	Study place	Setting	Study design	Number maternal Deaths reported
Ali, 1994	Oct. 1991-Dec. 1992	Jimma	Hospital based	Cross-sectional study	22
Gaym, 2000	1990-99	Jimma	Hospital based	Retrospective chart review	235
Hailu <i>et al.</i> , 2009	Dec. 2005-May 2006	Tigray	Hospital based	Cross-sectional study	34
Negussie & Mesfin, 2009	Sep. 2002-Aug. 2006	Jimma	Hospital based	Retrospective chart review	87
Girma <i>et al.</i> , 2013	Jul.2009-June 2010	Gamo-Gofa	Hospital based	Retrospective chart review	79
Yaya <i>et al.</i> , 2014	2006-Dec. 2010	Gamo-Gofa	Community based	Cross-sectional study	49
Yaya <i>et al.</i> , 2015	2010	Gamo-Gofa	Community based	Birth registration	53
Gebrehiwot & Tewolde, 2014	May 2011-Oct. 2012	Four regions	Hospital based	Cross-sectional study	206
Godefay <i>et al.</i> , 2015	May 2012-Sep. 2013	Tigray	Community based	Cross-sectional study	51
Godefay <i>et al.</i> , 2015	May 2012-Sep. 2013	Tigray	Community based	Case-control study	62 cases/ 248 controls
Prata <i>et al.</i> , 2012	Aug. 2010-Aug. 2011	Tigray	Community based	Vital registration	4
Deneke <i>et al.</i> , 2014	2007-2010	SNNP	Hospital based	Retrospective Chart review	127
Kassie <i>et al.</i> , 2014	Jan. 2010-Apr. 2012	Jimma	Hospital based	Cross-sectional study	6
Tesfaye, 2015	June 2013-Mar. 2015	DireDawa	Facilities based	Cross-sectional study	45
Chufamo <i>et al.</i> , 2015	1 Jan.-31 Dec. 2013	Jimma	Hospital based	Prospective cohort study	6
Gessesew & Melese, 2002	21 Apr. 1993 -30 Mar. 2001	Adigrat	Hospital based	Retrospective chart review	25
Wolde <i>et al.</i> , 2011	Apr. 2009-Mar. 2010	Jimma	Hospital based	Cross-sectional study	2
Worku <i>et al.</i> , 2013	Dec. 2011-Aug. 2012	Dabat District	Community based	Prospective cohort study	1
Gessesew & Barnabas, 2009	Jan. 2006-Dec.2008	Tigray	Facility based	Retrospective chart review	17
Berhan & Endeshaw, 2015	2008-2013	SNNP	Hospital based	Retrospective cohort study	51
Kelly <i>et al.</i> , 2010	1999-2008	Guraghe	Hospital based	Retrospective cohort study	71
Legese <i>et al.</i> , 2016	Jan. 2010-Dec. 2014	Jimma	Hospital based	Case-control study	120 cas 480 controls
EPHI, 2016	2013-2015	National	Community based	National MDSR	387
Assefa, 2016	2010-2015	National	Community based	HDSS	101

Direct causes of deaths: Direct causes were identified as the main cause of maternal death in most studies included in this systematic literature review (Table 3). The share of direct causes ranged from 83% in the

national maternal death surveillance response (MDSR) system report (20) to 94.9% in a study conducted in Jimma (14). When we look at the patterns of each cause of maternal death, hemorrhage is the leading cause of

mortality, followed by hypertensive disorders of pregnancy (HDP) and sepsis, especially in the recent years. On the other hand, the contribution of obstructed

labor and abortion seem to have decreased over the follow-up period, 2011-2016 (Table 3).

Table 3: Ranking of main direct causes of maternal deaths based on 16 studies

	Year of report	Hemorrhage	Obstructed labor	Sepsis	HDP	Abortion
Ali, 1994	1991-1992	3	2	4	NA	1
Gaym, 2000	1990-1999	4	1	3	5	2
Kellyet <i>al.</i> , 2010	1999-2008	2	1	4	3	5
Negussie & Mesfin, 2009	2002-2006	4	1	2	5	3
Hailuet <i>al.</i> , 2009	2005-2006	2	4	1	3	4
Gessesew& Barnabas, 2009	2006-2008	2	1	NA	NA	NA
Yayaet <i>al.</i> , 2014	2006-2010	2	3	1	3	4
../..../Sytematic Review/Progress reports/Data Extraction form.xlsx - RANGE!_ENREF_12	2007-2010	2	1	3	4	5
Denekeet <i>al.</i> , 2014	2009-2010	1	2	3	5	4
Girmaet <i>al.</i> , 2013	2010	1	4	2	3	NA
Yayaet <i>al.</i> , 2015	2011-2012	1	3	4	2	5
Gebrehiwot & Tewolde, 2014	2010-2014	1	NA	NA	2	NA
Legese, 2016	2012-2013	1	NA	NA	2	3
Godefayet <i>al.</i> , 2015	2013-2015	1	4	3	2	5
Tesfaye, 2015	2013-2015	1	4	3	2	5
EPHI, 2016	2010-2015	1	4	2	3	5
Assefa, 2016						

NA= information not available; HDP = Hypertensive disorders of pregnancy

Hemorrhage

Hemorrhage refers to both ante partum hemorrhage (APH) and postpartum hemorrhage (PPH). Hemorrhage is one of the leading causes of maternal deaths, standing first in eight of the articles reviewed in this study (17, 18, 20, 24, 27, 29, 31, 33). The magnitude of hemorrhage-induced maternal deaths ranged from 9.8% to 50.6% of all causes of maternal deaths. The results of the national MDSR report, and the health and demographic surveillance system (HDSS) report, reveal that more than half of the

maternal deaths are attributed to hemorrhage (20,31). Using the random effects model, the overall pooled proportion of maternal deaths attributed to hemorrhage was 29.9% (95% CI: 20.28%-39.56%). Although not statistically significant, according to the sub-group analysis, the proportion of hemorrhage-attributed maternal deaths increased from 24.34% (95% CI:14.00%-34.67%) in the earlier period of the study (1990-2010) to 38.98% (95% CI: 26.94%-51.02%) in the latter period (2011-2016) (Figure 2).

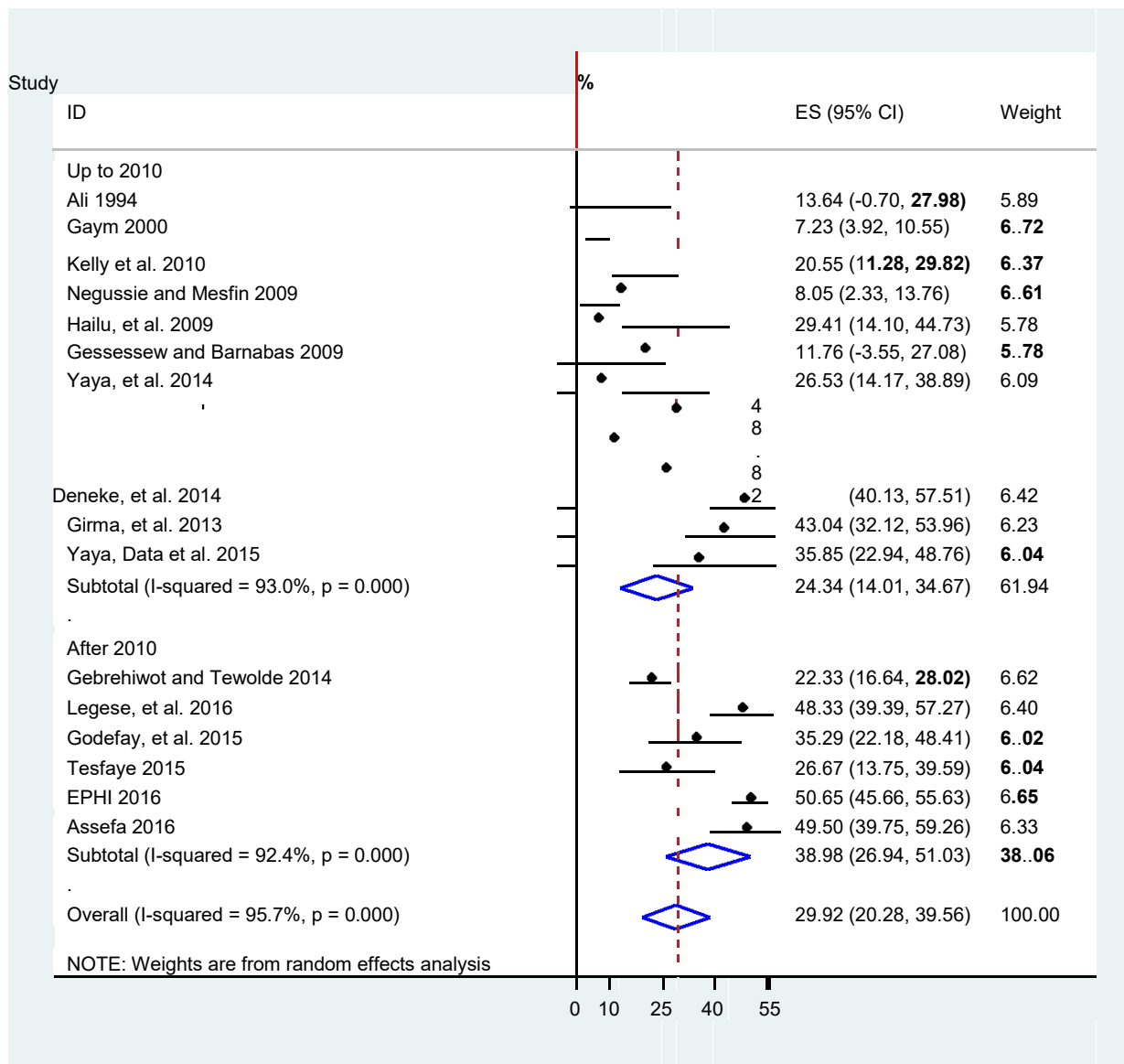


Figure 2: The pooled rate of maternal deaths attributed to hemorrhage, based on 16 studies

Obstructed labor/ruptured uterus

Three studies included both uterine rupture and obstructed labor, and reported them separately as causes of death (13, 15, 17). Others reported either one of them, while the remaining two articles documented uterine rupture alone (14,16). Six articles reported obstructed labor (19-22, 24, 27), while another three mentioned prolonged labor as a cause of maternal death (13, 17, 28). We have combined cases of obstructed labor with cases of ruptured uterus to compute the pooled proportion of maternal deaths attributed to obstructed labor. Accordingly, the pooled proportion of maternal deaths caused by obstructed labor was 22.34% (95% CI: 15.26%-29.42%) (Figure 2).

Meanwhile, most studies reveal that obstructed labor is contributing to the death of significant number of

mothers, after hemorrhage, while facility-based studies carried up to 2010 reveal obstructed labor as the first cause of maternal deaths (13, 14, 21, 22). The subgroup analysis shows that the proportion of maternal deaths attributed to obstructed labor has significantly decreased from 26.56% (95% CI: 15.82%-37.30%) in the studies from 1990-2010, to 9.94% (95% CI: 5.79%-14.09%) in the studies conducted from 2010 onwards (Figure 3). For instance, Gaym's study at Jimma hospital documented that obstructed labor contributed about 33.2% of maternal deaths (14). In contrast, the recently initiated national maternal death surveillance and response (MDSR) and the report of six HDSSs put obstructed labor as the fourth leading direct cause of maternal death, followed by sepsis, accounting for 6.7% and 7.9% of maternal deaths, respectively (20, 31).

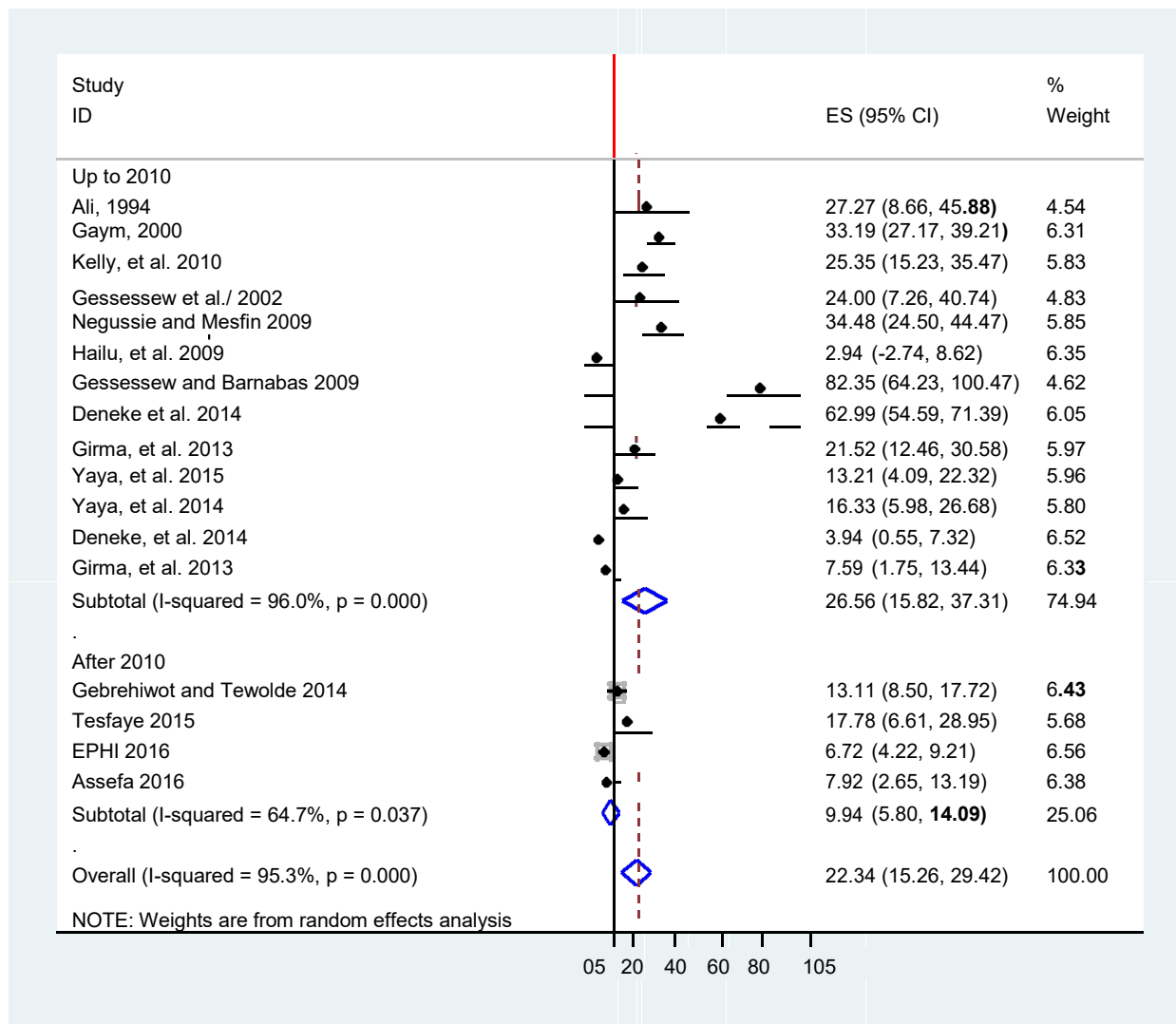


Figure 3: Pooled proportion of maternal deaths attributed to obstructed labor, based on 17 studies

Hypertensive disorders of pregnancy

Maternal death due to hypertensive disorders of pregnancy (HDP) occurs because of raised blood pressure during pregnancy, labor or postpartum. Six articles included in this review were able to document eclampsia as a cause of maternal death (1, 11, 13, 14, 22, 25); five identified the broader HDP as a cause of maternal death (20, 21, 24, 27, 33); and pregnancy-induced hypertension was mentioned as a cause in four articles (19, 27, 29, 31). One article each showed pre-eclampsia (17) and convulsions (28) as the cause of maternal death. The study conducted in 2000 (14) revealed only 5 (3.8%) of deaths compared with 23 (19%) (29) deaths that were attributed to eclampsia/pregnancy-induced hypertension. A study conducted among women admitted with HDP

documented 51 maternal deaths, of which 78.4% were attributed to eclampsia (11).

The overall pooled proportion of maternal deaths caused by HDP was 16.9% (95% CI: 11.2%-22.6%). Even though it is not statistically significant, the pooled proportion of HDP-caused maternal deaths was higher in the most recent studies (2011-2016) compared to those conducted prior to 2011 (Figure 4). The most recent studies (20, 24, 33) put HDP as the second leading cause of maternal deaths, after hemorrhage. A national hospital-based study conducted by Gebrehiwot& Tewolde (2014) put HDP as the second leading cause of maternal mortality, claiming 41 (19.9%) lives (33).

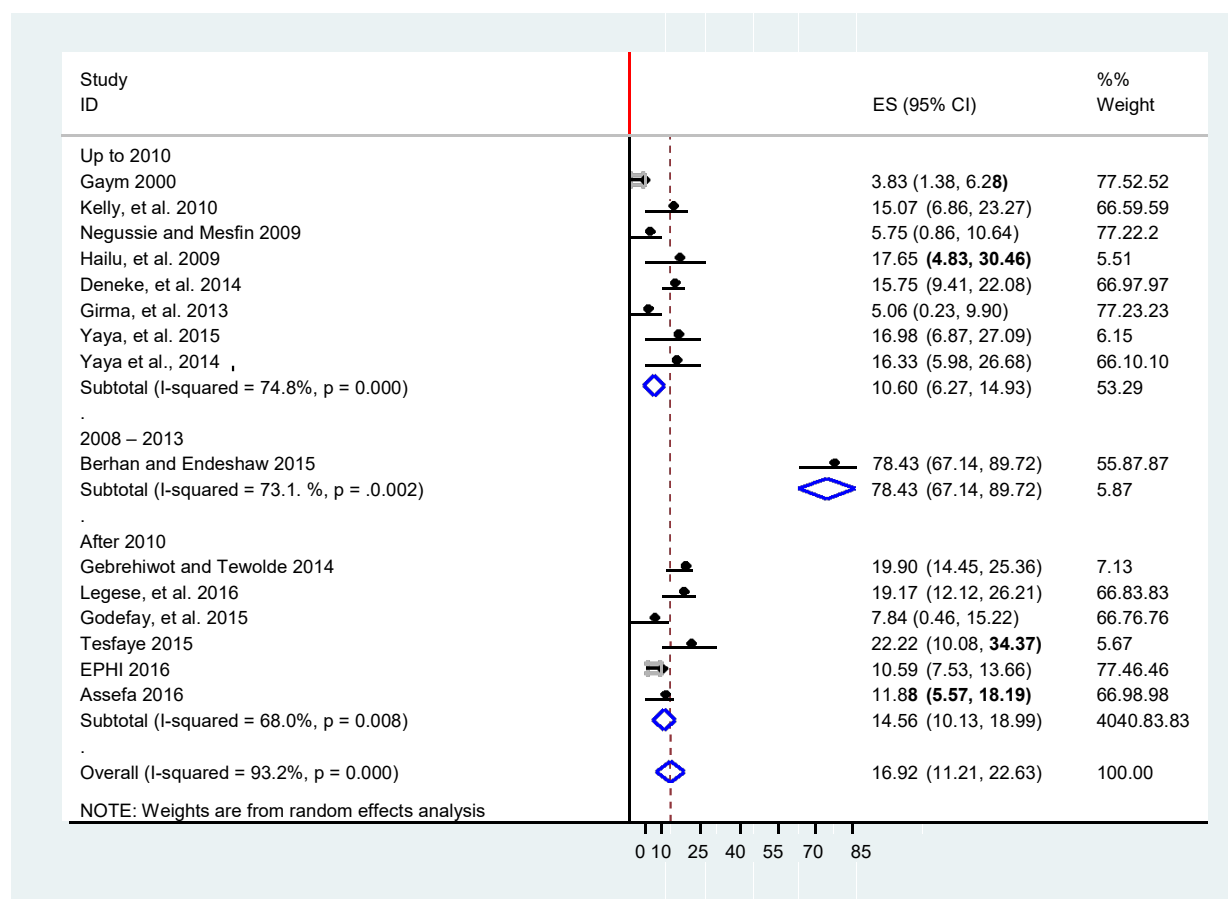


Figure 4: The pooled proportion of maternal death caused by hypertensive disorder of pregnancy based on 15 studies

Puerperal sepsis

The pooled proportion of maternal deaths accounted for by puerperal sepsis was 14.68% (95% CI: 10.56%-18.8%) (Figure 5). Puerperal sepsis was documented as the third leading cause of death (following obstructed labor and abortion) in the period 1990 to 1999, contributing about 20% of all maternal deaths in a study conducted in Jimma (14). Similarly, another study conducted in the same area documented sepsis as being responsible for the lives of a quarter of maternal

deaths (22). Moreover, the national MDSR also reported sepsis as the third largest cause, accounting for about 8.8% of maternal deaths (20). The report from six HDSS sites put sepsis as the second leading cause of death, after hemorrhage (31). The sub-group analysis shows that there was no statistically significant difference in the proportion of maternal deaths attributed to puerperal sepsis in recent studies (after 2010) compared to the earlier studies (Figure 5).

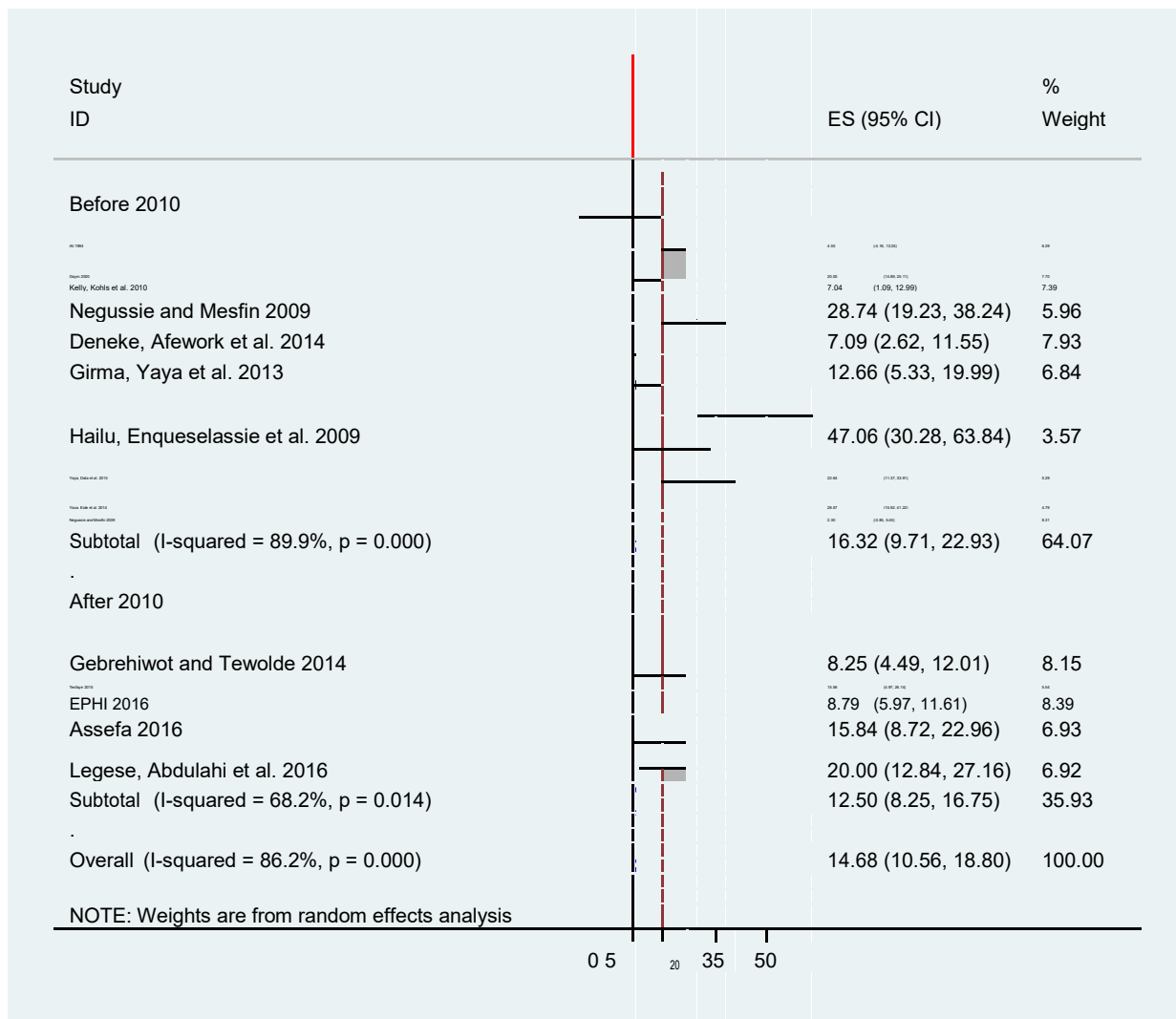


Figure 5: The burden and rank of puerperal sepsis as a cause of maternal death, based on 15 studies

Abortion

The oldest study, which was conducted in 1994 by Ali in Jimma, revealed unsafe abortion as the leading cause of maternal death (32). Another study, conducted by Gaym in 2002, retrospectively reviewed medical charts for 10 years. This showed abortion as the second leading cause of maternal deaths, accounting for over a quarter (26.8%) of the maternal deaths of women admitted to Jimma hospital (14). Another study conducted in the same hospital nine years later showed abortion as the third leading cause of maternal deaths, after obstructed labor and sepsis, which contributed about 15% of all maternal deaths (22). The pooled proportion of maternal deaths caused by abortion was

8.6% (95% CI: 5.0%-12.18%) (Figure 6). However, the toll of abortion has been reducing, as documented in different studies conducted in recent years (2011-2016) (18, 20, 28, 31, 33). The sub-group analysis shows that it has reduced from 11.14% (95% CI: 4.73%-17.54%) in the studies conducted before 2011 to 5.38% (95% CI: 2.46%-8.29%) in the studies conducted after 2010 (Figure 6). For instance, the National MDSR report in 2016 indicated that abortion contributed to only 2.3% of all maternal deaths (20). Similarly, a community-based study conducted by Godefay and colleagues showed that only three of the 51 maternal deaths were attributed to abortion (18).

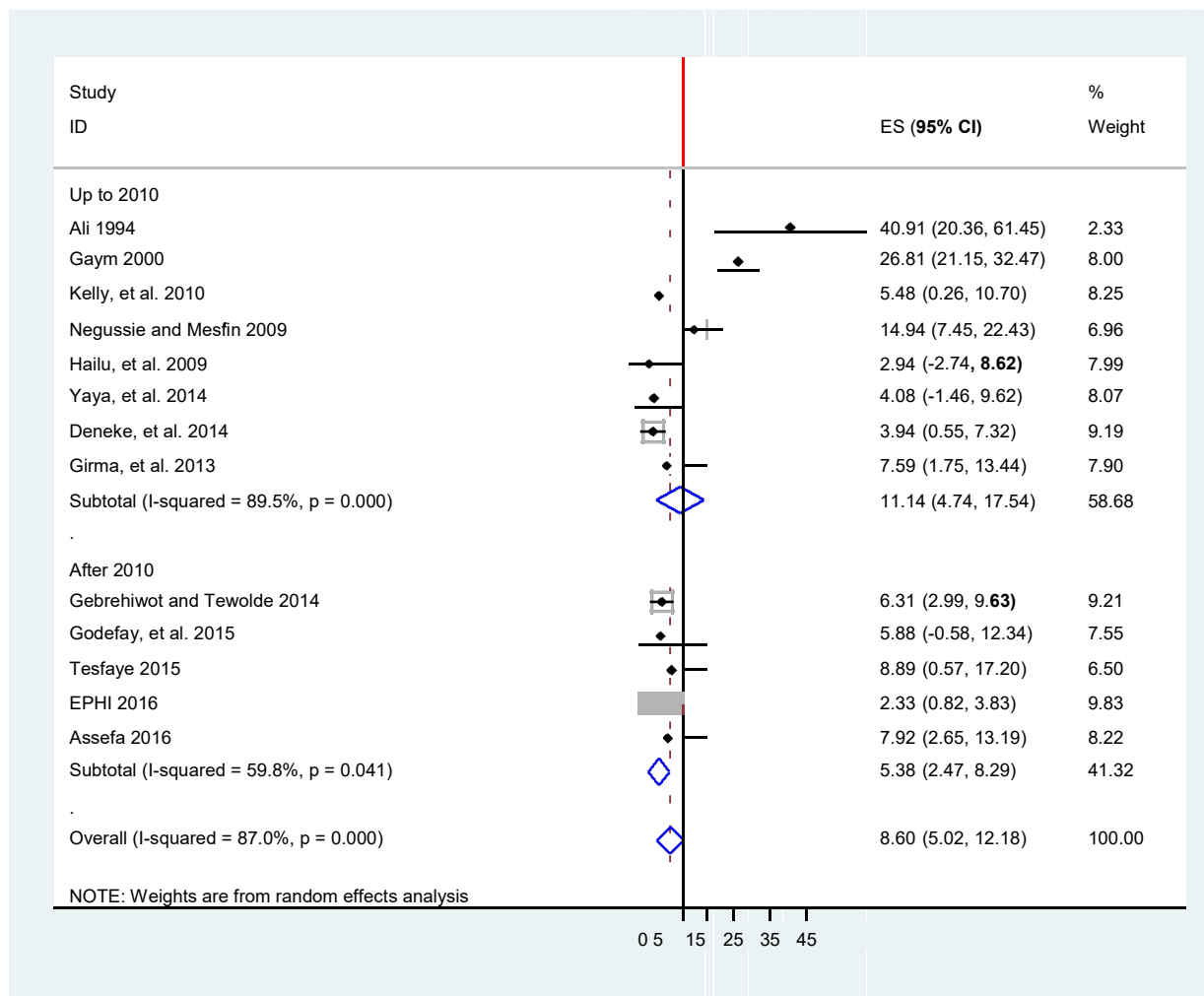


Figure 6: The pooled proportion of maternal deaths attributed to abortion, based on 13 studies

Other direct causes of maternal deaths

Besides the above mentioned main direct causes, other direct causes were also reported by the studies under the present review. These include ectopic pregnancy

(14, 22, 33), hyper emesis gravidarum (13), and premature rupture of membrane and intrauterine fetal deaths (28) (Table 4)

Table 4: Burden of other direct causes of maternal death from all maternal deaths, based on eight studies

Authors	Year of event	Causes	N (% of MDs)
Gaym, 2000	1990-1999	Ectopic pregnancy	3(1.2%)
Negussie & Mesfin, 2009	2002-2006	Ectopic pregnancy	2(2.3%)
Gebrehiwot & Tewolde, 2014	2011-2012	Ectopic pregnancy	2 (1.0%)
		Any form of embolism	8(3.9%)
		Severe anesthesia-related complication	2 (1.0%)
Deneke <i>et al.</i> , 2014	2007- 2010	Gestational trophoblastic disease	1 (0.5%)
		Hyperemesis gravidarum	3(2.3%)
Legese <i>et al.</i> , 2016	2010-2014	Post-term pregnancy	2(1.6%)
EPHI, 2016	2013-2015	Direct others	32(8.3%)
Deneke <i>et al.</i> , 2014	2007- 2010	PROM	2(1.6%)
	2007 - 2010	IUFD	3(2.3%)
Assefa, 2016	2010-2015	Direct others	7(6.9%)

PROM = premature rupture of membrane; IUFD = intrauterine fetal death

Indirect causes of maternal deaths: Most of the studies included in the present review documented malaria (13,14,18,20-22,32,33) and anemia (18,20,21,28,33) as the most common indirect causes of maternal death. The national MDSR also showed that 18.6% of maternal deaths were due to anemia. The overall pooled proportion of maternal deaths attributed to anemia and malaria were 10.39% (95% CI: 4.79%-15.98%) and 3.55% (95% CI: 1.63%-5.47%), respectively (Figures 7 and 8). According to the sub-

group analysis, although not statistically significant, the proportion of maternal deaths attributed to anemia increased from 5.88% (95% CI: 1.72%-10.04%) in the studies conducted up to 2010 to 13.18% (95% CI: 5.93%-20.42%) in the recent studies (Figure 7). In contrast, the share of malaria-caused maternal deaths decreased from 5.30% (95% CI: 1.52%-9.07%) in the period up to 2010 to 2.24% (95% CI: 0.85%-3.63%) in the period after 2010 (Figure 8).

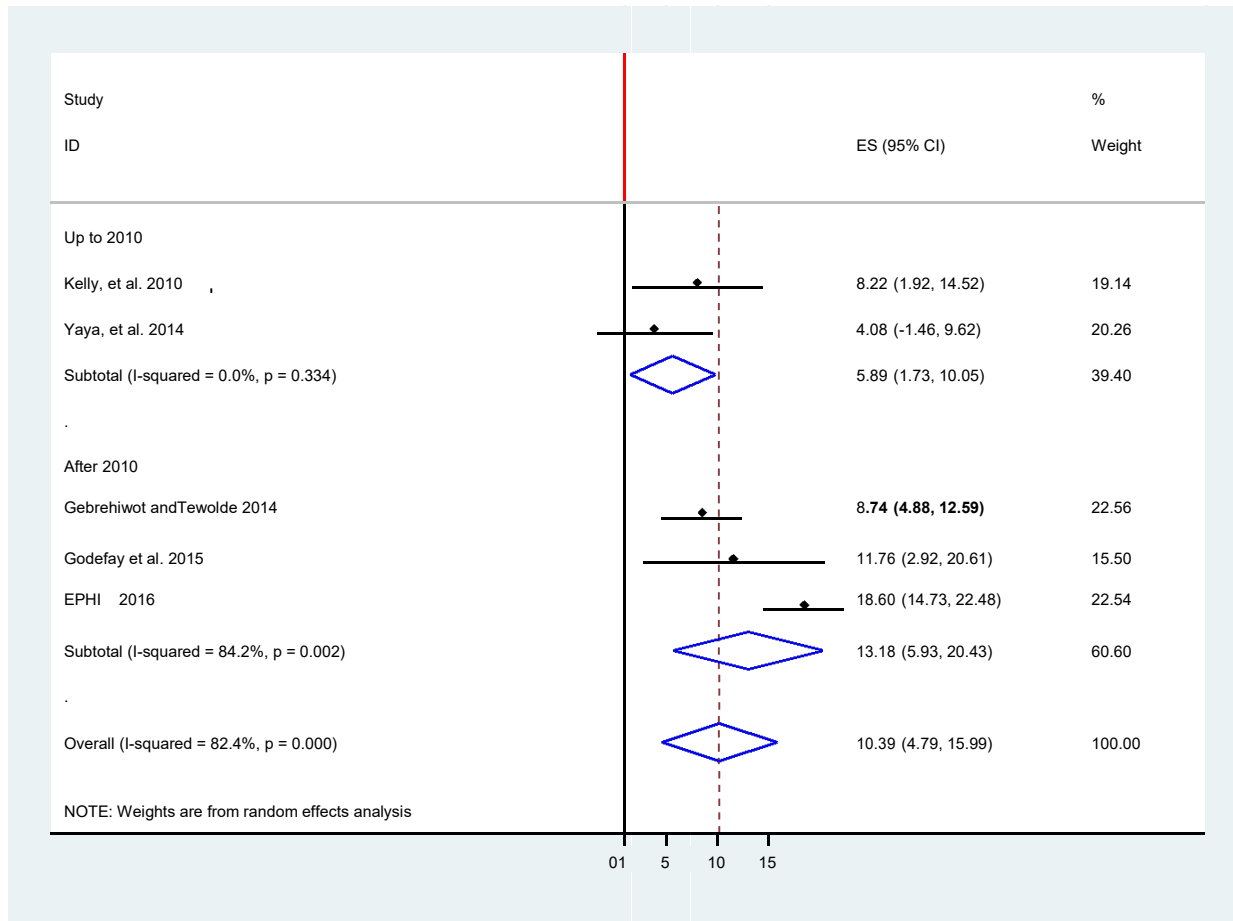


Figure 7: The pooled proportion of maternal deaths attributed to anemia, based on five studies

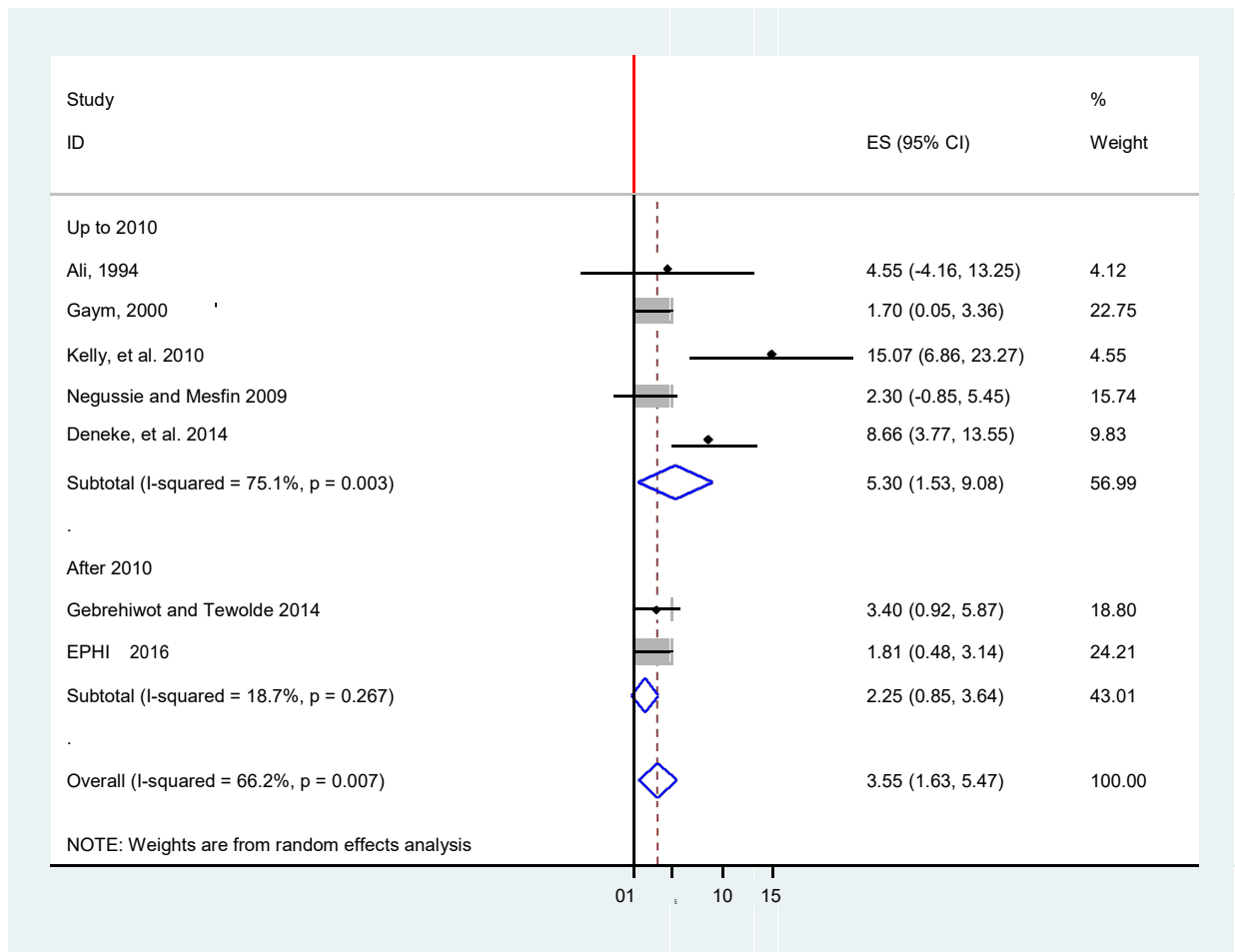


Figure 8: The pooled proportion of maternal deaths attributed to malaria, based on seven studies

In addition, HIV/AIDS (13, 18), tuberculosis (14, 18, 20) and other pre-existing diseases(13, 14, 21, 32, 33),including, cardio-pulmonary conditions, hepatic

and renal failures, diabetes, intestinal obstruction, pneumonia and relapsing fever, have been reported to contribute to causes of maternal death (Table 5).

Table 5: The burden of indirect causes of maternal death among maternal deaths, based on 11 studies

Authors	Year of event	Indirect causes	N (% of all MDs)
EPHI,2016	2013-2015	HIV	4(1.0%)
Godefay <i>et al.</i> , 2015	2012-2013	HIV/AIDS and malaria	1(1.96%)
		Pulmonary TB	5(10%)
EPHI,2016	2013-2015	TB	1(0.3%)
Ali, 1994	1991-1992	Intestinal obstruction and pneumonia	1(4.5%) for each
Gaym, 2000	1990-99	Infectious hepatitis	3(1.27%)
		Cardiac disease, diabetes	1(0.44%)
		Miletus, intestinal obstruction, pneumonia, and pulmonary TB	for each
Kelly <i>et al.</i> , 2010	1999-2008	Cardiac disease	2(2.74%)
		Relapsing fever	1(1.37%)
Deneke <i>et al.</i> , 2014	2007-2010	Other indirect causes (3CHF,1RVI, 1 anemia)	5(3.9%)
Gebrehiwot & Tewolde, 2014	2011-2012	Other (cardiac, hepatic, renal, pulmonary failure)	24 (11.7%)
Legese <i>et al.</i> , 2016	2010-2014	Other types of pre-existing diseases	40(33%)
Tesfaye, 2015	2013-2015	Others indirect (not specified)	4(9%)
Deneke <i>et al.</i> , 2014	2007/2008-2009/2010	Others indirect (not specified)	6(4.7%)
Yaya <i>et al.</i> , 2015	2010	Others indirect (not specified)	6(5.45%)
EPHI,2016	2013-2015	Others indirect (not specified)	55(14.2%)
Gessesew & Barnabas, 2009	2006-2008	No reason	1(5.88%)

TB = tuberculosis; CHF = congestive heart failure; RVI = retroviral infection

Gaps contributing to maternal deaths: Three of the studies included in this review attempted to identify gaps contributing to maternal deaths. Partner involvement in maternal health care acquisition and being a member of a women development army (WDA) –volunteers willingly involved in the promotion of safe motherhood – were reported to have protective effects in relation to maternal death. Women who were not members of a WDA (AOR=2.07;95% CI:1.04%-4.11%), and those whose husbands or partners had below-median scores for involvement during pregnancy (AOR=2.19;95% CI: 1.14%-4.18%),were almost twice as likely to die of causes of maternal death compared to their counterparts (30).

The presence of other pre-existing diseases was also reported to increase the risk of maternal death (29,30). For instance, according to Godefay *et al.* (30), women with a pre-existing history of other illness (OR= 5.58; 95% CI: 2.17%-14.30%) had more than five times higher odds of maternal death (30). Similarly, the study by Legese *et al.* reveals that mothers with pre-existing diseases had about 10 times higher odds of death (AOR=9.63;95% CI: 3.13%-29.58%) (29).The risk of death was also found to be 8.4 times higher among mothers admitted due to eclampsia (HR=8.4; 3.48%-20.15%) compared to those with pre-eclampsia (11).

The age of mothers is also highlighted as a risk for death (20,29). According to the study by EPHI, despite higher parity, the risk of maternal death was higher for mothers aged 35 and above, accounting for 21.2% of all deaths (20). Similarly, Legese *et al.*(29)found that the risk of maternal death among mothers aged 20-34 years was about 70% lower than those women aged 35 and above (AOR= 0.29;95% CI: 0.11%-0.79%). Furthermore, Berhan & Endeshaw found that the risk of maternal death among grand multiparous women (i.e. a woman who has had five or more previous pregnancies) was about three times higher (HR=2.8; CI: 1.13-6.78) than among primigravid women (a woman who is pregnant for the first time) (11).

Furthermore, contraceptive use (OR=2.58;95% CI: 1.37%-4.85%) (30)and a history of antenatal care (ANC)(HR=2.3; 1.19%-4.38%) (11) were also found to be protective factors against maternal death. Mothers from rural areas were shown to have 2.5 times higher odds of death (AOR =2.59;95% CI:1.00%-6.72%) compared with those from urban areas(29).

It is also to be noted that mothers who were referred from health centers and other health institutions had four to six times higher odds of death compared with those who were not referred(29).

A few of the articles (11,19,20,27,33) highlighted that delays contribute to maternal deaths. According to the national MDSR report, delay one (delay for seeking maternal care) was reported in 287(65.5%) of maternal deaths (20). Hailu *et al.* document that patient factors such as delayed care-seeking, home delivery while having a bad obstetric history, and a lack of ANC follow-up was observed in 81.3% of maternal deaths (19). Similarly, Gebrehiwot & Tewolde document delayed care-seeking in 66.9% of maternal deaths (33).

In addition, delay two – delay in accessing care during obstetric emergencies, which is partially accounted for by a lack of transport – was documented as a contributing factor to maternal deaths in Ethiopia (19,20,27,33). The national MDSR report documented delay two (i.e.) in 38.3% of maternal deaths in Ethiopia (20), whereas the study by Gebrehiwot & Tewolde, based on a review of 10 hospitals, documented delay two in 61% of maternal deaths (33). Lack of transport from home to health facility and the absence of comprehensive obstetric care were contributory factors to maternal deaths in two studies. In addition to delay one (delay in seeking) and two (delay in accessing), significant numbers of mothers who died experienced delay three (delay in receiving care during obstetric emergencies). The national MDSR report, Hailu *et al.*, and Gebrehiwot *et al.* document delay three in 36.4%, 87.5%, and 40.3% of maternal deaths, respectively (19,20,33). These were explained by staff incompetency, staff attitude, service inadequacy, treatment delay(19), and delayed referral from health facility(33).

Discussion

Maternal mortality rates have been significantly reduced at global levels, although Ethiopia could not achieve this specific MDG. Specifically, over the period 2005 to 2015, deaths due to maternal hemorrhage and abortion decreased by 16.6% and 23.1%, respectively (34).

According to the present systematic review, direct causes of maternal death represent the largest share of the maternal deaths in Ethiopia. This has also been documented in the national MDSR (20), where the proportion attributed to these causes is 83%. Evidence from other systematic reviews also support this finding, ascribing nearly three-quarters of maternal deaths to direct causes (35-37).

Of all the causes, hemorrhage (29.9%; 95% CI: 20.28%-39.56%) represents the highest share of maternal deaths. Three in 10 of the maternal deaths over the period of study were caused by hemorrhage. Furthermore, as reported by some of the community-based studies included in the review (23,34), the pattern of hemorrhage-attributed maternal deaths seems to have been increasing over time.

Our pooled proportion of maternal deaths attributed to hemorrhage is comparable with a previously conducted systematic review in Ethiopia (22%)(9) and global and

regional estimates of hemorrhage-caused maternal deaths(35). Worldwide, although the highest absolute reduction of maternal deaths was documented in deaths attributed to maternal hemorrhage, similar to our findings, hemorrhage remained the leading cause of maternal mortality(35,38,39), claiming 27.1% of all maternal deaths (35). Similarly, hemorrhage was also documented as being the leading cause of maternal death in Africa and Asia (39). In Rwanda, the leading cause of maternal deaths were PPH and obstructed labor –22.7% and 12.3%, respectively (40). Studies in Pakistan(41), Cameroon(42) and Mozambique (43) have also shown hemorrhage as the leading cause of maternal death, followed by HDP, sepsis, and obstructed labor.

The toll of maternal death from obstructed labor is not uniform in the reviewed literature. It is documented differently, as ruptured uterus, prolonged labor, obstructed labor and mal-presentations. According to the World Health Organization's worldwide estimates, obstructed labor is among the least of all the direct causes of maternal death, accounting for 2.8% of all deaths (35). However, it is one of the most common causes of maternal death in Africa (40). In our study, nearly a quarter (22.34%; 95% CI: 15.26%-29.42%) of maternal deaths reported from 1990 to 2016 resulted from obstructed labor/ruptured uterus. Although the period prevalence of obstructed labor-caused maternal deaths is high, its share seems to have been decreasing over time; it significantly declined from 26.56% (95% CI: 15.82%-37.30%) in the studies conducted from 1990-2010 to 9.94% (95% CI: 5.79%-14.09%) in the studies conducted from 2011 onwards. Similarly, a previous systematic review conducted in the country documented a reduction in the share of abortion and obstructed labor over the period of the study(9).

Over the period of our study (1990-2016), the pooled proportion of maternal deaths attributed to HDP was 16.9% (95% CI: 11.2%-22.6%). Similarly, from a previous systematic review, 19% of the maternal deaths were attributed to HDP (9). Moreover, HDP was the second leading cause of maternal deaths, contributing to 14% of maternal deaths worldwide (35).

Based on the global burden of disease estimate in 2013, the burden of sepsis has significantly reduced, resulting in the highest percentage of reduction in maternal deaths(44). Worldwide, 10.7% of maternal deaths are attributed to sepsis (35). In the present review, sepsis was one of the top direct causes of maternal deaths, accounting for 14.68% (95% CI: 10.56%-18.8%) of all maternal deaths. Most of the reviewed studies put sepsis as the second (22,27,31) or third (13,14,17,20,24) most common cause of maternal deaths.

In this study, unsafe abortion accounted for 8.6% (95% CI: 5.0%-12.18%) of all maternal deaths that occurred in Ethiopia from 1990 to 2016. This is comparable with the proportion of worldwide abortion-caused maternal deaths (7.9%), estimated for the period from 2003 to

2012(35). The proportion of abortion-caused maternal deaths decreased from 11.14% (95% CI: 4.73%-17.54%) in the studies conducted up to 2010, to 5.38% (95% CI: 2.46%-8.29%) in the studies conducted after 2010. Moreover, the reduction of abortion-caused maternal deaths was significant over the last two decades (9).

The indirect causes of maternal death coexisted with most of the direct causes of maternal deaths. For instance, a study in Mozambique documents the coexistence of HIV infection, malaria or anemia in more than 40% of maternal deaths caused by abortion, ectopic pregnancy and sepsis (43). In our review, anemia (10.39%; 95% CI: 4.79%-15.98%) and malaria (3.55%; 95% CI: 1.63%-5.47%) were the leading indirect causes of maternal deaths. Worldwide, in the period from 2003 to 2009, maternal deaths attributed to indirect causes were estimated to account for 27.5% of all maternal deaths (35). In 2006, anemia contributed to 3.7% to maternal deaths in Africa (39). Although we did not pool the magnitude of indirect causes in our review, there were also maternal deaths attributed to HIV/AIDS, tuberculosis, cardiac diseases, diabetes, intestinal obstruction, pneumonia and relapsing fever, as well as hepatic, renal, cardiac and pulmonary conditions.

In 2006, HIV was estimated to claim 6.2% of all maternal deaths in Africa (39). Globally in 2012, approximately 1.6% of all maternal deaths were attributed to HIV/AIDS (45). A study carried out in Tanzania documented that HIV attributed to 3.8% of maternal deaths (37).

Based on the few articles included in this review that document individual behavior, environmental and health system related gaps contributing to maternal death, the level of partner involvement during antenatal care, women's participation in WDA and contraceptive use were indicated as protective factors. On the other hand, having other pre-existing diseases, age, parity and rural residency were found as risk factors of maternal death. Maternal age is documented as a significant predictor of maternal death; the risk of death in women aged 45-49 is about 9.5 times higher than those aged 20-24 (44). A study conducted in Senegal and Mali found a higher risk of postpartum hemorrhage among women aged over 35 years, those women with pre-existing chronic diseases, pre-partum severe anemia, forceps or vacuum delivery, and birth weight greater than 4kg(46).

In addition, different factors contribute to maternal death (11,19,20,27,33). These could be explained in terms of the delay model. This systematic literature review documented the presence of delays in the health care-seeking behavior of women, contributing to complications and maternal death (19,33). Based on the national MDSR report, delay one (delay in care-seeking) was reported in 287(65.5%) of maternal deaths (20). Access to comprehensive obstetric service (delay two) was also documented as a contributing factor to maternal deaths in Ethiopia.

Distance and lack of transport were the most cited reasons for delay two (19,20,27,33). For instance, delay two was documented in 38.3% of maternal deaths in Ethiopia (20). Another study based on a review of 10 hospitals, documented delay two in 61% of maternal deaths (33). Moreover, significant numbers of mothers who died of pregnancy-related deaths experienced delay three, lack of receiving timely obstetric care. The national MDSR report, and studies conducted by Hailu *et al.* and by Gebrehiwot & Tewolde, document delay three in 36.4%, 87.5%, and 40.3% of maternal deaths, respectively (19,20,33). The reported delay three cases were mainly due to delayed treatment decisions and lack of appropriate treatment (19,33). This is also documented in other African countries (37,40,47). Studies in Tanzania and Nigeria document delayed referral, and delays in receiving appropriate treatment, respectively, as the main contributing factors to maternal death (37,47).

Limitations of this study

The results of this review should be interpreted with caution, since most of the included studies were facility based or record reviews. Moreover, there are limited nationwide studies –limited in scope and coverage, including the national MDSR report, which did not include the maternal death reviews from the emerging regions of Ethiopia. In addition, due to data incompleteness, outcome misclassification may have been inevitable, leading to over- or under-estimation of the direct and indirect causes. Furthermore, issues of potential publication bias are inevitable, and articles with a low quality-appraisal score were not excluded from the study. Although we used the random effect model and sub-group analyses, our pooled estimates could have been affected by the heterogeneity observed in the studies.

Conclusions

It is possible to conclude that the majority of maternal deaths in Ethiopia are attributed to direct obstetric causes, mainly to hemorrhage, HDP, sepsis, obstructed labor, and abortion. The role of indirect causes of maternal deaths, resulting from anemia, malaria and HIV/AIDS, is also considerable. There has been a statistically significant reduction of obstructed labor-caused maternal deaths over the period of the study. Besides, there has been an absolute reduction in abortion- and malaria-caused maternal deaths over the period of the study. On the other hand, the share of maternal deaths caused by hemorrhage, HDP and anemia increased in the recent studies (2011 onwards).

Furthermore, the three delays – delays in seeking (delay one), accessing (delay two) and receiving (delay three) care for obstetric emergencies, and other different individual, and health service-related factors – are gaps contributing to maternal death.

Most of the available evidence is health facility-based, thus community-based studies documenting all possible causes of maternal deaths should be encouraged. Overall, the review shows the importance of comprehensive nationwide registration of the causes

of maternal deaths in order to reveal the precise trends of the causes and individual behavior, environmental and health system related gaps contributing to maternal death in Ethiopia.

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