Measuring and Understanding Maternal Mortality in Georgia

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TABLE OF CONTENT

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ANC	Antenatal Care
AOR	Adjusted odds ratio
ASDR	Age-standardized death rate
BMI	Body Mass Index
BTN	Beyond the Numbers
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIS	Commonwealth of Independent States
CME	Continuing Medical Education
CPR	Contraceptive Prevalence Rate
COR	Crude odds ratio
CRVS	Civil Registration and Vital Statistics
CVD	Cardiovascular disease
EECA	East Europe and Central Asia
EU	European Union
FSU	Former Soviet Union
GBD	Global burden of disease
GERHS	Georgia Reproductive Health Survey
GDP	Gross Domestic Product
HIC	High income country
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICD-MM	ICD for Maternal Mortality
IDP	Internally displaced person
IHD	Ischemic heart disease
IEDSS	Electronic disease surveillance system
IRB	Institutional Review Board
LEPL	Legal public entity of law
LMIC	Low and middle-income countries
MDG	Millennium Development Goal
MDR-TB	Multidrug-resistant-tuberculosis
MMR	Maternal Mortality Ratio
MMEIG	Maternal Mortality Estimation Inter-Agency Group
MoLHSA	Ministry of Labor, Health and Social Affairs
NCD	Non-communicable disease
NCDC&PH	National Center for Disease Control and Public Health
OB/GYN	Obstetric/gynecological
PHC	Primary Health Care
PCVA	Physician-certified verbal autopsy
PPV	Positive Predictive Value
PPH	Postpartum hemorrhage
PE/E	Pre-eclampsia/eclampsia

PSDA	Public Service Development Agency
RAMOS	Reproductive Age Mortality Study
RR	Relative risk
RTI	Road traffic injury
SDG	Sustainable Development Goal
SRR	Standardized rate ratio
SSA	Social Service Agency
STEPS	STEPwise approach to surveillance
TB	Tuberculosis
TFR	Total Fertility Rate
TIAR	Total Induced Abortion Rate
TSA	Targeted Social Assistance
UHC	Universal Health Coverage
UN	United Nation
U.S.	United States
USAID	United States Agency for International Development
VA	Verbal autopsy
VSPI	Vital statistics performance index
WHO	World Health Organization

SUMMARY

The state of maternal health reflects national health care system development and economic, sociocultural and political agenda of the country. Maternal mortality ratio (MMR) and the causes of maternal death are two principal indicators of maternal health. The global maternal mortality target in the Sustainable Development Goals (SDGs) framework is <70 by 2030. The World Health Organization published "Strategies toward ending preventable maternal mortality" - a direction-setting report - outlines global targets and strategies for reducing maternal mortality under the SDGs. All countries should reduce their MMR by at least two-thirds from the 2010 baseline and achieve equity in maternal mortality levels for vulnerable populations at the subnational level. Achieving progress in reducing maternal mortality and improving health systems response to maternal health require better quality data, data-driven decision-making and local actions towards SDGs.

Most of the major causes of maternal deaths can be prevented or treated with effective and timely clinical interventions. This requires however, universal access to the provision of a quality continuum of care before, during and after birth.

Georgia still lags in reaching internationally agreed targets and compares negatively to other European countries to reducing maternal mortality. Despite of declared exigency of the issue, there is an obvious scarcity of scientific evidence on the accurate rates of maternal mortality, quality of mortality statistics in the country, including causes of maternal death and gaps in the care provided to the women during pregnancy and childbirth.

Based on the analysis of the data from the national Reproductive Age Mortality Study 2014, the study addresses several major research deficits regarding maternal mortality in Georgia. The thesis provides scientific evidence on leading causes of death among women of

reproductive age in Georgia and burden of maternal disorders in the overall mortality structure (Study I), as well as incidence, causes and level of underreporting of maternal mortality (Study II). Finally, the thesis identifies key factors in substandard obstetric care for early and late maternal deaths (Study III).

The study on the mortality patterns and trends of women of reproductive age in Georgia (Paper I) found NCDs (non-communicable diseases; 69.6% or 53.1/100 000) to remain by far the leading causes of death, with cancer (45.2% or 34.5/100 000), being the most common cause, followed by injuries (18.6% or 14.2/100 000), and cardiovascular diseases (CVD, 13.2% or 8.8/100 000). Substantial underreporting of leading causes of death, with the majority (84%, $p<0.05$) miscoded as undetermined cause category, was a significant finding of the study.

The study (Paper II) on maternal mortality incidence, causes and underreporting found an overall MMR (early and late maternal deaths) of 40.3 per 100 000 live births, which is a 38.5% reduction compared to the MMR of 65.6 per 100 000 live births found in 2006. A total of 36 pregnancy-related deaths were identified. Among these, 23 (63.9 %) deaths were classified as maternal, directly or indirectly caused by pregnancy and 13 (36.1%) as deaths from co-incidental causes. Of the 23 maternal deaths, 15 (65.2%) were early and eight (34.8%) late deaths. The four leading causes were sepsis, hemorrhage, pulmonary embolism and preeclampsia/eclampsia. Among the indirect maternal death causes, cancer was the most common (n=3). All 36 pregnancy-related deaths included in our study were officially reported in the vital registration system, whereas only 85.7% were reported in 2006. The study documented 39.1% overall underreporting of maternal deaths by the official statistics, with late and indirect deaths being commonly unreported.

Study of audit of early and late maternal deaths (Paper III) found suboptimal care provided in 87% of early maternal deaths. Suboptimal care, assumed to have made a difference to the outcome, was documented in 67% of late maternal deaths due to direct obstetric causes.
The findings of this research indicated NCDs to be the greatest threat for women's health during fertile years. Cancer being the leading cause, and breast cancer remaining the principal cause of premature mortality, underscores the urgent need to adopt a life-course and whole health systems response, and multisectoral approaches to curb the epidemics of NCDs.
Similar to many developed countries, Georgia will likely see an obstetric transition from mostly direct to more indirect causes of maternal mortality. This emphasizes that addressing NCDs and their effects on maternal health becomes increasingly urgent. The gains observed in maternal health outcomes across Georgia will continue to require further improvements in quality and safety at multiple levels of the health system. The direct maternal deaths comprising most of the cases in our study indicate that improvements of quality of obstetrical care is warranted.

Finally, reliable data documenting the health risks of women during their reproductive years is of critical importance to inform evidence-based health policies. This requires strengthening the national civil registration and vital statistics system as well as systematic and regular national analyses and monitoring of maternal deaths, particularly to understand inequities that lead to disparities in maternal health outcomes.

LIST OF PAPERS

The present thesis is based on three scientific papers, all published:

Paper I

Lomia N*, **Berdzuli N*,** Sturua L, Kereselidze M, Topuridze M, Pestvenidze E, Stray-Pedersen B. Int J Womens Health. Leading causes of death of women of reproductive age in the Republic of Georgia: findings from the National Reproductive Age Mortality Survey (2014). 2018;10:437–452.

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Paper II

Berdzuli N, Lomia N, Staff AC, Kereselidze M, Lazdane G, Jacobsen AF. Maternal Mortality in Georgia: Incidence, Causes and Level of Underreporting: A National Reproductive Age Mortality Study 2014. Int J Womens Health. 2020:12 277–286

Paper III

Berdzuli N, Lomia N, Staff AC, Lazdane G, Pestvenidze E, Jacobsen AF. Audit of Early and Late Maternal Deaths in Georgia: Potential for Improving Substandard Obstetric Care. Int J Womens Health. 2021;13:205-219.

1. INTRODUCTION

1.1. Global and regional overview of maternal mortality and determinants of maternal health

The state of maternal health reflects national health care system development and economic, sociocultural and political agenda of the country. Maternal mortality ratio (MMR) and the causes of maternal death are two principal indicators of maternal health. Sustainable Development Goals (SDGs) adopted by the United Nations (UN) set a target to reduce the global maternal mortality ratio (MMR) to less than 70 per 100 000 live births. The national target for maternal mortality in the SDG framework is that all countries should reduce their MMR by at least two-thirds from the 2010 baseline and achieve equity in maternal mortality levels for vulnerable populations at the subnational level [1-2].

The global estimates indicate that between 2000 and 2017, the maternal mortality ratio (MMR, number of maternal deaths per 100,000 live births) dropped by about 38% worldwide. Compared with other causes, the overall proportion of deaths to women of reproductive age (15–49 years) that are due to maternal causes (PM) was estimated at 9.2% in 2017 – down by 26.3% since 2000 [3].

Maternal mortality is still unacceptably high in some countries. Despite the greatest reduction achieved, Sub-Saharan Africa and Southern Asia accounted for approximately 86% (254 000) of the estimated global maternal deaths in 2017. Clear majority of maternal deaths (94%) occur in low-income countries, and most could have been prevented (*Table 1*) [3].

Table 1. *Estimates of maternal mortality ratio, number of maternal deaths and lifetime risk of maternal death, 2017*

Region/sub-region/other grouping	MMR	Number of MD	Lifetime risk of MD
World	211	295 000	190
Sub-Saharan Africa	542	196 000	37
Northern Africa	112	7 600	260
Western Asia	55	3 000	650
Central Asia	24	390	1400
Southern Asia	157	58 000	250
Eastern Asia	28	5 300	2200
South-Eastern Asia	137	16 000	320
Latin America and the Caribbean	73	7 700	640
Australia and New Zealand	7	26	7 800
Oceania (excluding Australia and New Zealand)	129	380	210
Europe	10	740	6500
Northern America	18	760	3100
Small island developing States	210	2 600	190
Least developed countries	415	130 000	56

The low estimated MMR (<100 maternal deaths per 100 000 live births) in 2017 was reported for Australia and New Zealand; Europe; Northern America; Central, Eastern and Western Asia; and Latin America and the Caribbean.

Overall global MMR decreased between 2000 and 2017 by 38% and reduction was reported almost everywhere except Northern America. During this period the global MMR declined yearly by 2.9%. The highest overall percentage reduction in MMR between 2000 and 2017 (59%) was reached by Southern Asia, which presents 5.3% annual reduction in MMR. Northern Africa, Eastern Asia, Europe and Central Asia reduced their MMRs by half during this period. Sub-Saharan Africa also reduced its MMR by 38% since 2000, as well as world's low-income countries, where it declined by 46%. Ten countries with the highest MMRs in 2017 all have <5% annual reduction in MMR between 2000 and 2017 [3] (*Table 2*).

Table 2: *Comparison of MMR in 2000 and 2017*

Region/sub-region/other grouping	MMR estimates in 2000	MMR estimates in 2017	Overall % change in MMR between 2000 and 2017	Average annual rate of reduction in MMR between 2000 and 2017
World	342	211	38.4	2.9
Sub-Saharan Africa	878	542	38.2	2.8
Northern Africa	244	112	54.1	4.6
Western Asia	81	55	32.4	2.3
Central Asia	49	24	52.0	4.3
Southern Asia	384	157	59.2	5.3
Eastern Asia	56	28	49.9	4.1
South-Eastern Asia	214	137	36.0	2.6
Latin America and the Caribbean	95	73	23.0	1.5
Australia and New Zealand	8	7	11.0	0.7
Oceania (excluding Australia and New Zealand)	223	129	42.0	3.2
Europe	20	10	53.3	4.5
Northern America	12	18	-52.2	-2.5
Small island developing States	249	210	15.7	1.0
Least developed countries	763	415	45.6	3.6

In the European Region [4], maternal mortality has decreased substantially over the past 20 years [5-6]. While MMR is relatively low in comparison with other regions of the world, the region reveals a wide variation between countries. The highest national maternal mortality rate in the Region is now estimated to be 20 times the lowest, reflecting significant inequalities in maternal health in the Region. To reach the SDG 3 and particularly its Target 3.1, each country should establish or strengthen its system for collection and timely dissemination of health data to have a clear and true picture of the levels and causes of maternal deaths, as currently comparing is a big challenge. Therefore, to reduce maternal mortality and improve health systems and programs the better quality of data is crucial.

Postpartum hemorrhage (PPH), pre-eclampsia/eclampsia (PE/E), and sepsis due to direct maternal infections are the main causes of all maternal deaths globally [7-8] and are major contributors to severe maternal morbidity [9]. Although these direct causes remain the most

important cause of maternal death, non-communicable diseases, such as cardiovascular, cancer and other diseases emerge as an important contributor to maternal mortality in both developing countries and developed world [10-11].

Most of the major causes of maternal deaths can be prevented or treated with effective and timely clinical interventions. This requires universal access to the provision of a continuum of care before, during and after birth. However, even if a woman manages to access care in a health facility with a skilled birth attendant, substandard quality of care in pregnancy, and during and after childbirth, late referral, can be life-threatening. Moreover, many risk factors for maternal death may exist well before pregnancy and delivery. Social determinants such as place of residence, socioeconomic status and race/ethnicity as well as institutional factors such as national resource allocation, health system infrastructure and political accountability influence a woman's likelihood of dying from childbirth-related complications. Furthermore, health inequities should be considered from the human rights perspective. Unequal opportunities, unequal access to resources and power inequalities are an issue of social justice [12].

One of the targets linked to Goal 3 (Ensure healthy lives and promote well-being for all at all ages) of SDGs is to "achieve Universal Health Coverage (UHC) including financial risk protection, access to quality essential health care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all." UHC has been defined as all people receiving quality health services that meet their needs without being exposed to financial hardship [13].

Women and children are among those groups that gain most from UHC as they are largely affected by inequalities in access to health care. The benefit packages offered by UHC in most countries usually includes a set of services and access to care for pregnant women

before, during and after birth [14-15]. During the last two decades the majority of low and middle-income countries (LMIC) have achieved an increase in coverage for essential health services, including antenatal care, skilled care at birth and postnatal care. However, inequalities in access to care clearly demonstrates the differences between socio-economic groups, where those who need the most care are the least likely to receive it [16], masked by indicators that measure overall population coverage for an intervention. Poverty and lack of health care resources are the main factors that prevent women from receiving adequate health care services during their pregnancy and childbirth. Even where the services are officially free, hidden costs may add up to a substantial part of monthly income, or even several times monthly income, particularly costs of severe complications can have a catastrophic impact on household budgets.

Adding a dimension of quality of care produces further challenges. Quality of care is a critical component of ending preventable maternal mortality and a significant challenge in most countries. Quality of care is defined as provision of timely, reliable, equitable, efficient, compassionate, patient-centered care, with application of evidence-based standards to ensure patient safety and health worker satisfaction [17-19]. Further, enabling environments that promote evidence-based practices and leadership, governance and accountability for quality are important as is ensuring an adequate financing. The removal of financial barriers to care seeking and increasing financing for health are the two most important priority areas as the ability to pay is a significant determinant for utilization of health care services. Lack of financing, including innovative financing models, undermines the provision of quality and more effective, efficient and equitable care.

Having targets for maternal mortality reduction is important, but accurate measurement remains challenging and many maternal deaths still go unrecognized. Well-functioning civil

registration and vital statistics (CRVS) systems with good attribution of cause of death is a major challenge. Even in countries with complete and developed CRVS systems, MMR based on death registers alone fails to detect the overall magnitude of the maternal deaths because of reporting errors – whether underreporting or misclassification [20]. The most frequently miscoded or not reported deaths in routine reporting include those associated with abortion, early pregnancy deaths (resulting from ectopic or molar pregnancy), deaths later in the postpartum period, indirect maternal deaths and deaths that occur sometime after the end of pregnancy, especially where the death occurs in a non-obstetric hospital ward, such as in an intensive care or other specialized non-obstetric unit [21-22]. Estimating accurately maternal mortality necessitates a well-functioning maternal mortality surveillance system. Confidential death enquiries and multiple sources of death identification are often used to document and classify maternal deaths [11, 23]. Other periodic focused studies are also required to assess true magnitude of maternal mortality and to implement policies and strategies based on reliable data.

1.2 Georgia – country context

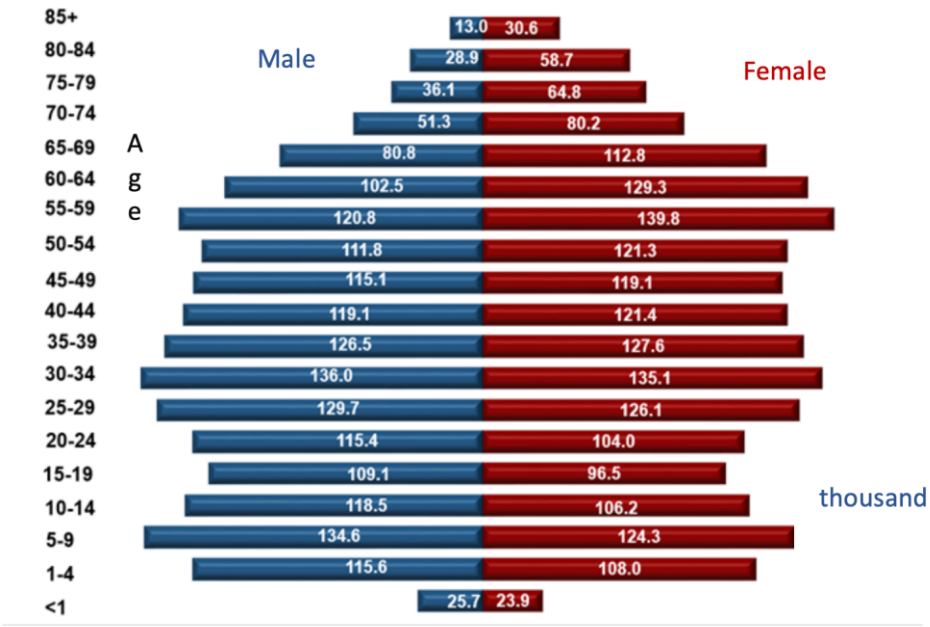
Georgia is an independent country with strategically important location – at the crossroads between Europe and Asia, bordered by Armenia, Azerbaijan, the Black Sea, Russia and Turkey. The officially reported population amounted to 3,716, 900 [24] in 2020. Key demographic characteristics and indicators provided in the *Figure 1* [25].

Figure 1: *Georgia – key characteristics*

GEORGIA		
POPULATION AND DEMOGRAPHICS		
Total Population	2020	3,716,900
Women of reproductive age (15-49 years)	2020	824,400
Adolescents	2020	426,000
Under-five year old	2020	266,800
Total number of birth	2019	48,296
Key indicators		
Maternal Mortality Ratio	2019	28.9/100 000 livebirth
Stillbirth Rate/1000 birth	2019	9.4/1000 birth
Neonatal Mortality Rate	2019	5.2 /1000 livebirth
Under-five Mortality Rate	2019	9.4 /1000 livebirth
Adolescent Mortality Rate	2019	38.8/100 000 population
Total fertility rate	2019	2.01 livebirth per woman

The country witnessed dramatic demographic transformation, including an unprecedented shrinking of the population during the last decades due to the extensive out-migration. An increasing share of population (59%) reside in urban area, explained by the ongoing intense urbanization process. This disproportional geographic distribution is illustrated by almost one-third of the population concentrated in the capital city due to the higher job availability. Sex distribution is almost even, with a slight predominance of female population (52%). Importantly, women of reproductive age (15-44 years) constitute almost one-third (29%) of the total population and more than a half (55%) of the female population [25] *(Figure 2*).

***Figure 2**: Population pyramid, 2019*



Georgia became part of the Soviet Union in 1921 and remained in the grasps of Soviet stagnation and dependence for 70 years. Country regained independence from the collapsing Soviet Union in 1991, followed by a challenging transitional decade marked with political and social crisis, war, economic collapse, corruption and crime [26]. Just in the five years following independence, the gross domestic product (GDP) experienced unprecedented fall by three-fourth, with a skyrocketing increase in annual inflation rate [27]. An acute economic collapse, with rapidly shrinking resources, resulted in a drastic fall of health expenditures as a share of total public expenditure, from 13 % in 1991 to 0.5% in 1994 [28].

A rapid ascent of economic parameters and restoration of macroeconomic stability started with the change of government in 2003 through the “Rose Revolution”. A young, enthusiastic and western-oriented new government opened a stage for rigorous, profound and ambitious chain of reforms, grounded on free market-regulated economy to condense bureaucracy, eliminate corruption and a rapid economic development. Results were quick and impressive: improved

financial stability and economic indicators, better governance, enhanced living conditions, and a better business climate [29].

Both development and economic indicators showed stable and steady raise over the next two decades. The GDP per capita increased from 853 USD in 2002 to 4698 USD in 2019 [30]. According to the country classifications by income level, Georgia moved from low-middle income country to the upper- middle income group with a Gross National Income (GNI) per capita (current US$) reaching 4130 as of July 1, 2019 [31]. Yet, economic progress has not benefited all segments of the Georgian population. Reduction of the poverty and unemployment is a key economic and social challenge for the country. Almost one-fifth of the population (19.6%) lived below the absolute poverty threshold in 2019 [32]. Covid-19 pandemic and related emergency lockdown and social distancing measures introduced by the country to control the epidemic likely will exacerbate existing challenges and further inequalities, putting at risk those that are already most disadvantaged. The true scale of the crisis remains to be seen and so extraordinary measures will be required from the government for recovery efforts and building back better.

Georgia benefited for decades from having the highest life expectancy among the Soviet republics and later among the Commonwealth of Independent States (CIS). By 2019, the country documented life expectancy rate was 74.0 years (69.7 for males and 78.2 for females). The most recent General Population Census in 2014 documented a 25% fall in the population number since the independence. This resulted in revised population estimates, modified denominator and therefore, population-based indicators, including life expectancy at birth [33-34].

1.3 Health system development overview. Key milestones impacting maternal health care in Georgia

For seventy years the Georgian healthcare system—mode of operation, administrative structure, principles of financing —represented an integral part of the entire Soviet healthcare system, grounded on the so called Semashko model, a highly centralized, integrated, and hierarchically organized state-funded health care to all citizens. After emerging from the collapsing Soviet Union in 1991, Georgia inherited the model with a 100 % publicly financed and publicly owned health service delivery. Yet, the hereditary costly health system, built on highly specialized hospital-based curative care, became unaffordable with the discontinuation of a centralized Soviet financing and collapsed rapidly and irreversibly soon after the country's independence. The physical condition of health care facilities, including maternity hospitals deteriorated, as did a medical technology and equipment [35]. The health infrastructure was poor, obsolete (majority of maternity hospitals constructed before 1940), over-spaced, with excessive number of underutilized beds that were unaffordable to maintain. Essential equipment and supplies were insufficient, often outdated, and dysfunctional [36]. Persisting challenges with running water and electricity supply posed a significant threat to the safety and quality of health services at all hospitals, including maternity clinics.

The challenges were present not only with infrastructure, but with human resources as well. The health system was bloated with excessive supply of unevenly distributed, under-utilized and inadequately managed medical staffing in all areas of health care. No system was in place for Continuing Medical Education (CME) of health professionals. The state certificate of medical activity was permanent, not linked to the system of continuous professional development.

The attempt to establish a CME system was made in 2001, yet the system was abolished soon, as it was inefficient, formal, sometimes a source of corruption, and did not serve a purpose of upgrading the knowledge/skills and broadening of professional expertise [37]. The density of doctors was one of the highest in the European Region. For example, the number of obstetricians/gynecologists was 35 per 100 000 population (2013) as opposed to an average of 15 per 100 000 population in the member states of the European Union (EU) [38].

Oversupply of doctors contrasted with critical shortage of nurses. In 2013, the number of nurses in Georgia was 341 as compared to 856 per 100 000 population in the EU [38]. The shortage of nurses was paralleled with the low status of middle-level health professionals deepened also by an absence of certification or licensing practices [39].

The supply of midwives during the Soviet time was sufficient and remained so few years after gaining independence. In 1997 there were 47 midwives per 100 000 population in Georgia vs average 42 midwives per 100 000 population in the WHO European Region. Yet, the number started decreasing sharply and reached 13 per 100 000 population in 2013 vs 40 per 100 000 population in the WHO European Region [40]. The fading popularity and low acknowledgement of the midwifery profession was a major contributor of observed negative trend.

Paralleling the decline in infrastructure and human resources, the delivery of obstetric services was suboptimal in newly independent Georgia. Until 2005, the country had been practicing "Soviet" obstetric care, not based on scientific evidence, often inhuman and using some of the practices harmful for both, mothers and babies. Women were delivering in large, obsolete and often freezing delivery rooms, three to five in the same room, without any privacy and family support, subjected to clinically unjustified overmedicalization, over-intervention (unacceptably

high rates of episiotomy, labor stimulation and labor induction). Poor obstetric practices lead to psychologically and physically traumatized mothers and babies, negative birth experience, non-evidence-based, suboptimal quality, costly obstetric and neonatal care with consequently deteriorated maternal and perinatal health outcomes [40].

The Maternal Mortality Ratio (MMR) raised sharply from 41/100 000 live births in 1991 to 70/100 000 live births in 1997 [28]. In response to the emerging crisis and existing profound challenges in the health care system, the first stage of Georgian Healthcare Reform package (GHR) was initiated with four core components:

- decentralization of health care management [41]
- initiation of health care privatization [42]
- prioritization of primary health care
- introduction of a new health care financing model: a shift from state-funded healthcare to social insurance coverage with program-based funding [43]. The program-based funding entailed a state subsidized compulsory perinatal care program [44], covering four antenatal care visits and delivery services.

Government endorsed 2000-2009 Health System Development Strategy included maternal and child health improvement as one of the key priorities. In addition to this strategy, the government developed a hospital sector restructuring plan to address challenges with infrastructure and medical technologies and to optimize national network of health facilities, all aiming to improve patient safety and quality of health services. However, the first health reform and hospital sector restructuring plan did not produce the expected results. The mandatory social health insurance system soon turned to be formal with a persistently underfunded program-based financing, including lack of funding for perinatal care [45].

A new wave of reforms was initiated with the change of government as a result of the Rose Revolution. Reforms were grounded on free market-regulated economy, aiming at reducing bureaucracy, combatting corruption and accomplishing rapid economic growth [46]. The reforms in the health sector included privatization of health care infrastructure – selling hospitals to private investors for redevelopment as modern hospitals, abandoning social health insurance and introduction of private health insurance – everyone expected to purchase coverage except for households living below the poverty line for whom insurance premiums paid from public funds, reduction of health sector regulation to an essential minimum with the core concept - "the market can and should replace the government's regulation" [47-51].

Some progress had been achieved in tackling poverty and stabilizing economy in the country with consequent improvement in overall health status and core maternal-newborn indicators. The MMR decreased from 47.8/100 000 live births in 2000 to 23.9/100 000 live births in 2005 according to the official statistics [25] (*Figure 3).*

Figure 3*: Georgia Maternal Mortality Ratio per 100 000 live births*

The privatization reform produced desirable result in terms of improving the obsolete infrastructure of hospitals, renewing equipment and supplies and minimizing informal payments for health services. However, the total privatization combined with profound deregulation led to some negative consequences, including suboptimal reporting and accountability by service providers; income-oriented private owners, with little focus on clinical outcomes, and with a major interest in minimized spending for the greatest profit; high concentration of healthcare facilities in big cities rather than in remote geographic areas; and monopolies by health care investors in specific geographic areas.

Simultaneously, with the new wave of health care reforms, Georgia introduced and institutionalized a WHO-developed package of evidence-based Effective Perinatal Care (EPC) principles through the USAID (United States Agency for International Development) supported Healthy Women in Georgia project. This initiative was regarded as a key milestone in a profound transformation of perinatal care services: from "Soviet" obstetric and neonatal practices into "family friendly" evidence-based maternity care. Important results were documented through project evaluation and included de-medicalization and evidence-based obstetric and neonatal care, postpartum hemorrhage reduction, improved infection prevention practices, positive birth experience (women delivering in individual, family friendly delivery rooms, with preserved privacy and dignity, accompanied by a close person, free choice of delivering positions), raised satisfaction of medical personal, and reduced costs for deliveries due to the less interventions and less complications [40].

After the parliamentary elections in 2012, adherent to the political commitment to protect the population from financial risks of health care costs and to reduce inequalities, the newly elected government of Georgia introduced Universal Health Care (UHC) extending the breadth of the coverage for the whole population [52]. Transition to the UHC model resulted in increased

access to health care services, improved financial protection with a reduction in out-of-pocket payments from 73% in 2012 to 57% in 2015 [33]. The introduction of UHC was accompanied by revitalization of universal coverage for antenatal and delivery services, which was not part of state-covered health services since the 2007 reform. An obstetric care package introduced in 2013 and currently in place includes a coverage for vaginal delivery in limit of 500 GEL (~ 165 USD) and cesarean section in limit of 800 GEL (~260 USD) [53]. Yet, the government funding for pregnancy and childbirth is not sufficient to cover the full cost of services. Co-payment is still required, and amount depends on the fee established by the individual health care facility.

The major milestone in 2015 was a systemic reform aimed towards improving perinatal care service delivery in Georgia - "Regionalization of Maternal and Neonatal Health Services" - a data-driven package of reforms to improve maternal and infant health outcomes (Order N01-2n) [33,54]. The reform envisioned creation of a comprehensive, coordinated and geographically structured system of stratified health care facilities according to their individual capacity and geographic location and provision of risk-appropriate perinatal care to all mothers and infants. Some of the result of this complex transformation process included assignment of levels for obstetrics and neonatal care (100 % of facilities), closer of facilities with low delivery volumes capabilities, and improvements of human resource capacity, infrastructure and equipment. The reform also led to improved perinatal outcomes with perinatal mortality reducing from 13.4/1000 births in 2015 to 12.1/1000 births in 2019, and maternal mortality from 32.2/100 000 live births in 2015 to 28.9/100 000 live births in 2019 [25].

The regionalization of perinatal care led to modification of licensing standards for perinatal care facilities. Designation of the level of care became valid for a defined period (2 years), therefore, health care facilities need to be constantly compliant with established requirements

[55]. Additionally, the regionalization reform was complemented by a revitalization of the CME system for perinatal care service providers, mandating all acting obstetricians/gynecologists and neonatologists to undergo the training program on annual basis for updating skills and knowledge and raising competence in evidence-based obstetric and neonatal care practices [56].

Important advancement was made in provision of antenatal care (ANC). In 2017, the national ANC protocol was revised and updated in line with WHO recommendations on antenatal care for a positive pregnancy experience [57-58]. Revised ANC protocol recommends transition from the minimum four antenatal visits into a more comprehensive eight visits pregnancy care model. Importantly, increased number of routine ANC visits was accompanied by a significant improvement in financing: state financing increased three-fold, from 55 GEL (~20 USD) to 180 GEL (~60 USD) coverage per pregnancy.

Georgia made significant progress in strengthening government oversight over and implementing chain of effective measures toward improving the quality of perinatal care. Specifically, selective purchasing of perinatal services linking contracting of maternal health care facilities with quality of services was introduced by the Social Service Agency (SSA) in 2017 [59]. Importantly, the country also introduced a comprehensive system for maternal and perinatal death reviews: developed maternal and perinatal death review tools, established panel of reviewers, trained pool of clinical experts in review techniques, and introduced practice for routine death review, results discussion and follow-up improvement measures.

Finally, National Maternal & Newborn Health Strategy (2017-2030) and a 3-year Action Plan (2017-2019) [60] represents a national roadmap to accelerate progress toward the 2030 maternal and reproductive health targets for Georgia. It lays the groundwork for country-led

implementation planning that drive the process of achieving the best possible health outcomes and ending preventable maternal and newborn deaths by 2030.

1.4 Stratified model of perinatal care service delivery in Georgia

Antenatal Care

Antenatal care services are provided through the extensive network of 291 health care facilities: either ANC department/room of outpatient clinics or ANC department of in-patient clinics [25]. The care for pregnant women of any complexity is delivered exclusively by licensed obstetrician/gynecologists with needs-based support from various specialists. The antenatal services are covered through the State Perinatal Care Program, which allocates a fixed amount of funds: 180 GEL per uncomplicated pregnancy. The national antenatal care guideline (adopted in 2017) recommends minimum 8 visits for routine pregnancy care with defined scope and content of services covered by the state (*Table 3).*

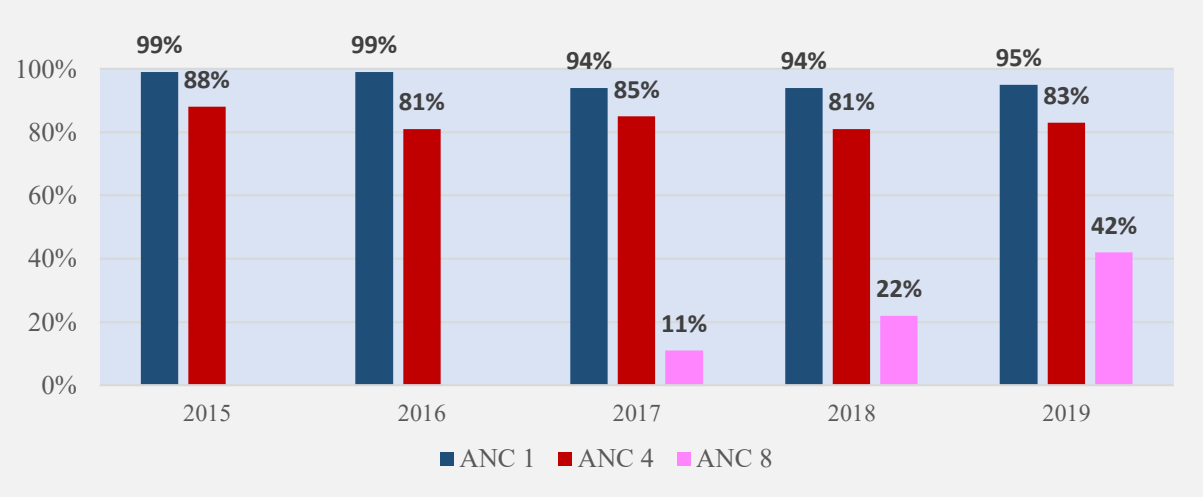
***Table 3**: Scope and content of services by ANC visits*

Antenatal Care Visits	
Visit I **< 12 6/7 gestational weeks**	• Pregnancy confirmation • Collection of personal and family history to detect pregnancy risk level; • Assessment of blood pressure and other vital functions; • Weighing, measuring, calculating body mass index; • Detecting developmental abnormalities of the genital tract if any • Preventing anemia and neural tube defects (iron and folic acid supplementation) • Defining pregnant women Rh and blood group • General blood test • Urine culture to screen for asymptomatic bacteriuria • Screening tests for Hepatitis B virus, Hepatitis C virus, HIV / AIDS and syphilis; • Ultrasound examination • Comprehensive counselling on: course of pregnancy, discomforts during pregnancy, danger signs, fetal development, risk-appropriate care principles, nutrition, healthy life-style etc.
Visit II **18 0 / 7-20 6/7 gestational weeks**	• Ultrasonographic screening at 18 0 / 7-20 6/7 weeks of pregnancy to detect fetal malformations • Assessment of blood pressure and vital functions • Assessment of pregnancy progress • Comprehensive counselling on: course of pregnancy, discomforts during pregnancy, danger signs, fetal development, risk-appropriate care principles, nutrition, healthy life-style etc.
Visit III **At 30 gestational weeks**	• Assessment of blood pressure and vital functions; • Assessment of pregnancy progress; • Test for proteinuria • Symphysis-fundal height measurement • Rescreening for anemia • RhD alloimmunization - anti-D immunoglobulin administration to non-sensitized Rh-negative pregnant • Screening for gestational diabetes • Comprehensive counselling on: course of pregnancy, danger signs, fetal development, risk-appropriate care principles, nutrition, healthy life-style, importance of breastfeeding etc.

Visit IV **At 32 gestational weeks**	• Assessment of blood pressure and vital functions; • Assessment of pregnancy progress; • Test for proteinuria • Symphysis-fundus height measurement • Comprehensive counselling on: course of pregnancy, danger signs, fetal development, risk-appropriate care principles, nutrition, healthy life-style, importance of breastfeeding etc.
Visit V **At 34 gestational weeks**	• Assessment of blood pressure and vital functions; • Assessment of pregnancy progress; • Test for proteinuria • Symphysis-fundus height measurement • Comprehensive counselling on: course of pregnancy, danger signs, fetal development, risk-appropriate care principles, nutrition, healthy life-style, importance of breastfeeding etc.
Visit VI **At 36 gestational weeks**	• Assessment of blood pressure and vital functions; • Assessment of pregnancy progress; • Test for proteinuria • Rescreening for anemia • Symphysis-fundus height measurement • Comprehensive counselling on: stages of labor/delivery, signs of labor start, danger signs, risk-appropriate care principles, nutrition, healthy life-style, importance of breastfeeding, postpartum family planning etc.
Visit VII **At 38 gestational weeks**	• Assessment of blood pressure and vital functions; • Assessment of pregnancy progress; • Test for proteinuria • Comprehensive counselling on: stages of labor/delivery, signs of labor start, danger signs, risk-appropriate care principles, nutrition, healthy life-style, importance of breastfeeding, postpartum family planning etc.
Visit VIII **At 40 gestational weeks**	• Assessment of blood pressure and vital functions; • Test for proteinuria • Vaginal examination • Offering labor induction at 41 0/7 weeks of gestation • Biophysical profile • Comprehensive counselling on: stages of labor/delivery, signs of labor start, danger signs, risk-appropriate care principles, nutrition, healthy life-style, importance of breastfeeding, postpartum family planning etc.

The utilization indicator of ANC services varies depending on the number of ANC visits. At least one ANC visit was used by 95% - 99% of pregnant women in 2015-2019. The utilization of minimum four visits was lower and ranged between 80% - 88% in the same period. The use of eight visits is still low but has an increasing rate: raising from 11% in 2017 to 42% in 2019 [25] (*Figure 4*).

***Figure 4**: Utilization of ANC services*



Importantly, a positive trend was documented in early utilization of ANC services (before 12 weeks of pregnancy), raising from 82% in 2015 to over 90% in 2019, likely attributed to the reduced financial barriers in accessing ANC services.

Obstetric Care

Obstetric care in Georgia is provided by a stratified network of private for-profit providers, with good geographic access ensured to at least basic perinatal care services (within 40-60 min drive from any location of the country). The childbirth is managed by a team of licensed obstetrician/gynecologists and midwives. According to the competency framework, obstetrician/gynecologists is present and responsible for the delivery process, no matter how complex or uncomplicated it is.

Health care facilities that provide obstetric care for the expectant women are classified based on functional capabilities. These facilities are organized within an established regionalized system of perinatal care. The system aims to ensure that every expectant woman and newborn has access to appropriate level of high quality, safe and effective care, before, during and after delivery at a right time and a right place.

With the perinatal care regionalization reform, stratified model adopted by the country, the risk and complexity of each pregnant woman is continuously assessed during pregnancy and referred for the childbirth to the health care facility with technical, human resources and functional capability based on woman's and fetus' needs.

Levels of obstetric and neonatal care

The stratification model in Georgian perinatal care system is grounded on the principles recommended by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) Guidelines for Perinatal care (7-th edition) [61]. Specifically, health care facilities providing obstetric care are organized around three levels of complexity interchangeably applying both numerical (Level I, Level II, Level III care) and the functional, descriptive designations (basic, specialty, and subspecialty care respectively) [54] (*Tables 4-6).*

***Table 4**: Scope of services and human resource requirement for Level I perinatal care facilities*

Level I (Basic care)	Provides basic delivery services for completely normal or deliveries with mild complication, has limited physical and clinical capacity
Obstetric services	• Manage uncomplicated pregnancy and labor according to the national guideline/protocol; • Manage mild obstetric complications; • Perform Cesarean section within 30 minutes after making decision under general or regional anesthesia; • Identify signs and symptoms of potential maternal problems; • Stabilize severe maternal complications before transfer to II or III level facility; • Perform timely referral of high risk pregnancies (facility should have a referral policy clearly defining the list of complications for which transfer must be made, specifying referral level); • Provide maternal care after delivery in case of uncomplicated labor and labor with mild complications.
Neonatal services	• Provide care of healthy full-term newborns (≥ 37 0/7), that don't need and are not expected to need special intervention in accordance with approved national guidelines and protocols; • Stabilize and provide care for sick infants and those born <37 0/7 week of gestation before their referral to the higher-level facility. • In case of need provide neonatal resuscitation at every delivery according to the national protocol.
Human resource	• Ob/gyn (24/7) • Midwife (24/7) • Neonatologist (can be on-call at night time) • Anesthesiologist (can be on-call at night time) • Nurse (24/7)

***Table 5**: Scope of services and human resource requirement for Level II perinatal care facilities*

Level II (Specialty care)	Level II units offer high level obstetric care for both normal uncomplicated deliveries as well as high risk pregnancies and all emergency pregnancy and delivery complications, which do not require subspecialized care.
Obstetric services	• Manage uncomplicated pregnancy and labor according to the national guideline/protocol; • Manage all maternal complications, which do not require subspecialized care according to the national/international guidelines and protocols; • Identify women with serious medical complications, requiring subspecialized care, stabilize them before transfer and perform timely referral to level III facility (facility should have a referral policy clearly defining the list of complications/conditions for which transfer must be made); • Provide postpartum care after uncomplicated and complicated labor and delivery.
Neonatal services	• Provide care for infants born ≥34 0/7 weeks gestation who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis; • Provide mechanical ventilation for brief duration (<24 h) or continuous positive airway pressure or both; • Stabilize infants born before 34 0/7 weeks gestation before transfer to a neonatal intensive care facility;
Human resource	• Ob/gyns (24/7) • Midwifes (24/7) • Neonatologists (24/7) • Anesthesiologists (24/7) • Nurses (24/7) • Pediatric cardiologist and pediatric surgeon (on-call) • General surgeon (on-call)

***Table 6**: Scope of services and human resource requirement for Level III perinatal care facilities*

Level III) (Sub-specialty care)	Level III facilities providing tertiary level maternity care manage most complicated pregnancies and deliveries, which require interdisciplinary care. This level maternities are located within tertiary multipurpose medical centers with capabilities for all medical and surgical specialties, intensive care etc. Level III neonatal units are characterized by having and operating a Neonatal Intensive Care Units (NICU)
Obstetric services	• Manage all kinds of maternal complications, provide highly specialized complex services for all pregnant and delivering women according to the national/international guidelines and protocols; provide comprehensive support by using high technologies and participation of multidisciplinary team; • Provide postpartum care after uncomplicated and complicated labor.
Neonatal services	Level II care plus: • Provide sustained life support; • Provide comprehensive care for infants born <34 0/7 weeks gestation and infants born at all gestational ages and birth weights with critical illness; • Provide prompt and readily available access to a full range of paediatric medical subspecialists; • Provide a full range of respiratory support that may include conventional and/or high-frequency ventilation and inhaled nitric oxide; • Perform advanced imaging, with interpretation on an urgent basis, including computed tomography, MRI, and echocardiography
Human resource	• Ob/gyns (24/7) • Midwifes (24/7) • Neonatologists (24/7) • Anesthesiologists (24/7) • Nurses (24/7) • Wide range of pediatric subspecialists (available within 30 min after the call): cardiologist, surgeon, neurologist, hematologist, endocrinologist, ophthalmologist, pulmonary specialist, gastrointestinal specialist, nephrologist; • Wide range of subspecialists to provide care for pregnant/delivering women (available within 30 min after the call): cardiologist, surgeon, neurologist, hematologist, endocrinologist, ophthalmologist, pulmonary specialist, gastrointestinal specialist, nephrologist, urologist, infectious disease specialist.

As of 2020, 78 health care facilities provide perinatal care services of different levels *(Figures 6-7)*.

***Figure 6**: Distribution of perinatal care facilities by levels of care, Georgia, 2020*

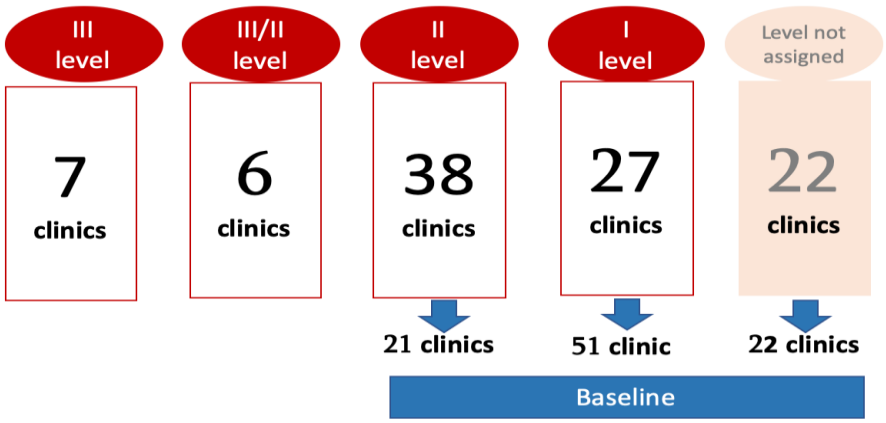
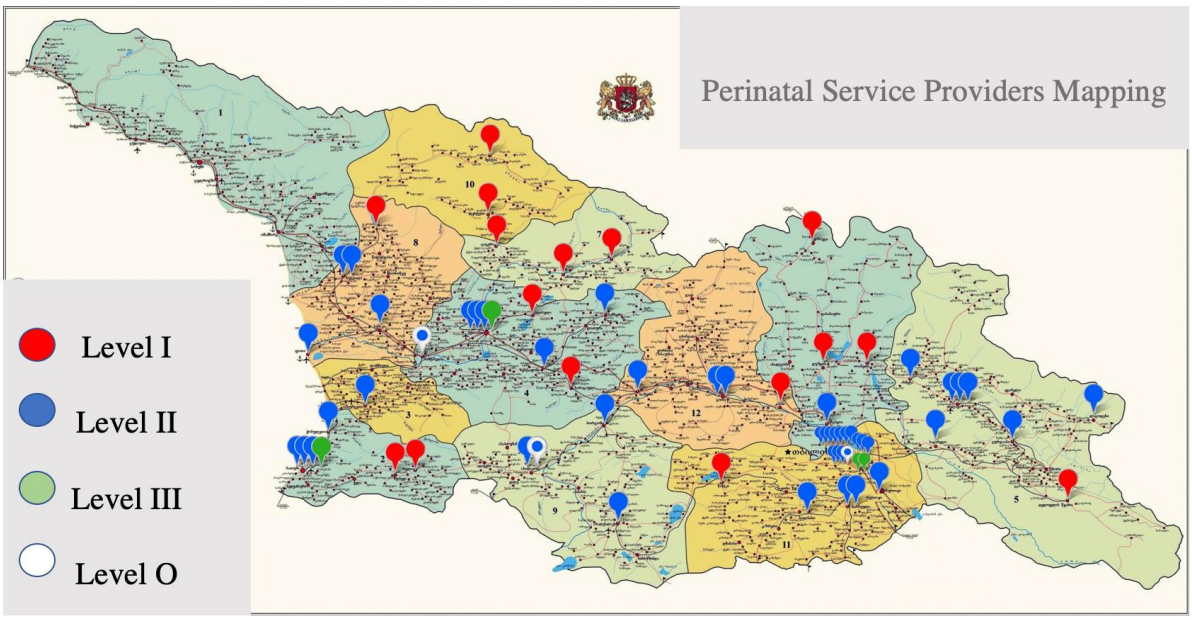


***Figure 7**: Geographic distribution of perinatal care facilities, Georgia, 2020*



2. RESEARCH RATIONAL

With over half a million women dying each year due to the complications of pregnancy and delivery, and majority of these deaths being preventable, reduction of maternal mortality remains in the heart of global health agenda and international development efforts. The longstanding commitment of countries to eliminate preventable maternal deaths and thus reducing maternal mortality ratio was encapsulated initially in the Millennium Development Goal and later in the Sustainable Development Goals of the United Nation. Yet, to succeed in accomplishing the set goals and to reduce maternal mortality, countries need to have accurate knowledge on the mortality statistics, causes of maternal death, quality of care provided, potential gaps in the system and service provision which may contribute to the death outcomes.

Georgia has made tangible progress in improving maternity care, nevertheless, the country still lags in reaching internationally agreed targets and compares negatively to other European countries in reducing maternal mortality. Despite of declared exigency of the issue, Georgia has scarcity of accurate rates of maternal mortality, causes of maternal death and systemic gaps in the care provided during pregnancy and childbirth, as well as good understanding of mortality statistics quality. The present study addresses several major research deficits regarding maternal mortality in Georgia and provides scientific evidence on:

- Maternal mortality indicators and trend over time
- Quality of mortality statistics
- Causes of maternal deaths
- Quality of care and factors contributing to substandard quality

2.1 Maternal mortality indicator. Millennium and Sustainable Development Goals

Maternal mortality is a global indicator, widely regarded as an overall measure of population health and wellbeing, indicator of human and health system development level and, finally, indicator of the status of the women in a society. Low maternal mortality ratios are thus pointers of high standards of health system development versus high mortality numbers indicative of broader challenges in health services, gender inequalities, and health systems in general.

Maternal mortality is commonly measured by the maternal mortality ratio.

$$MMRatio = \left(\frac{MD}{Births} \right) * 100000$$

Maternal mortality ratio (MMR) = Number of maternal deaths (MD) / Number of livebirths X 100,000.

Maternal mortality ratio is designed to express direct or indirect obstetric risk - the risk of woman to die once she gets pregnant. As such, the live birth rather than woman of reproductive age is used for the denominator in maternal mortality ratio indicator.

Unlike to the maternal mortality ratio, maternal mortality rate is a cause-specific death rate.

$$MMRate = \left(\frac{MD}{PYL^{f}} \right) * 1000$$

The measure is calculated by dividing number of maternal death in a period to the person years lived (PYL^{f}) - by women of reproductive age (normally 15 to 49) in a period.

Maternal mortality ratio rather than maternal mortality rate is commonly used to measure the maternal death worldwide and by countries. Maternal mortality ratio jointly with child mortality indicators is applied to set the health development goals globally.

Global Agenda for Millennium and Sustainable development. Progress in Georgia

After the Millennium Summit of the United Nations and signing of the United Nations Millennium Declaration by world leaders in September 2000, the set of eight international development goals - MDGs for the year 2015 were elaborated and adopted by the UN Member States. Georgian government, signatory to the MDGs, pledged to decrease infant and under-five mortality by two-thirds (MDG Target 4) and maternal mortality by three-fourths (MDG Target 5) between 1990 and 2015.

The country managed to accomplish MDG 4 target of reducing under-five mortality rate by two-third (i.e. 16/1000 live births). Under-five mortality rate declined from 48/1000 livebirths in 1990 to 12/1000 livebirths in 2015; during the same period infant mortality rate (IMR) reduced from 41/1000 live births to 11/1000 live births, and neonatal mortality rate (NMR) – from 25/1000 live births to 7/1000 live births.

Yet, Georgia failed to achieve the set MDG 5 target of reducing MMR by three -fourth (i.e. 16/100 000 live births). The MMR in 2015 was 32/ 100 000 live births – double the set target for MDG.

Despite accomplishments, the challenges existing in MDG era persisted to be unresolved, along with new and emerging health challenges. To address these, the UN General Assembly adopted a new Resolution "Transforming our world: the 2030 Agenda for Sustainable Development" [1], which transited the world into a more sustainable and robust route for global development for over the next fifteen years.

In 2015, the Georgian government committed to accomplish the United Nation's Sustainable Development Goals (SDG) and to reduce maternal mortality to 12/100 000 live births by 2030. While the pace of progress toward improving maternal health in Georgia has accelerated, the target set for SDG remains well out of reach.

2.2 Accurate measures of maternal death and quality of mortality statistics

Having accurate measures of maternal mortality is a key in identifying challenges, building a reliable evidence base and measuring progress and achievements toward improving maternal health outcomes. Accomplishing an ambitious SDG targets and reducing maternal mortality could not be accomplished unless every country takes bold and proactive measures in counting precisely every birth and every maternal death. Establishing accurate mortality statistics was identified as a cross-cutting priority for both MDG and SDG agenda and was number one out of ten stated recommendations of the Commission for Information and Accountability [62]. A new and robust accountability framework had been developed and proposed to ensure that results and resources are monitored and tracked, and all countries honor their commitments to accelerate path toward improvement of maternal health.

For implementing the proposed accountability framework, the Commission elaborated 10 specific, measurable, achievable and time-bound recommendations built upon the principle: better information for better results.

Recommendation 1

Vital events: By 2015, all countries have taken significant steps to establish a system for registration of births, deaths and causes of death, and have well-functioning health information systems that combine data from facilities, administrative sources and surveys.

Despite of the urgency of the issue, many countries still fail to accomplish well- functioning, integrated health information systems that have a potential to accurately count and register

every maternal death. Lack of capacity by countries to count births and deaths precisely and to identify correctly causes of maternal death has been named a "scandal of invisibility" [62].

Concerted efforts, political will, commitment and investments are required to establish solid maternal death registration systems capable to generate accurate and reliable data.

Methods of obtaining maternal mortality data

High income countries commonly have established advanced health information systems, where a civil registration represents a conventional source of maternal mortality statistics [63-64].

The low- and middle-income countries with limited capacity to register death and birth apply other methods for obtaining maternal mortality data. According to the systematic review study by the Liverpool Centre for Maternal and Newborn Health, six main methods were identified based on which low- and middle-income countries get the maternal mortality data [65].

Civil registration and vital statistics data

"Civil registration is defined as the continuous, permanent, compulsory and universal recording of the occurrence and characteristics of vital events pertaining to the population as provided through decree or regulation in accordance with the legal requirements of a country" [66].

According to the WHO, "a well-functioning civil registration and vital statistics (CRVS) system registers all births and deaths, issues birth and death certificates, and compiles and disseminates vital statistics, including cause of death information. It may also record marriages and divorces [67]." Yet, availability, accuracy, reliability, completeness and coverage of the birth and death data in the CRVS is suboptimal in many countries. According to the WHO estimates, as much as two-thirds of deaths are never registered and are therefore not captured

in the vital statistics system. Therefore, alternate data sources are used to calculate maternal mortality.

Health facility data

Majority of developing countries utilize health facility data for calculating MMR. Sources of data from health care facilities entail routine reports produced by facilities on regular bases, sentinel sites, reports issued by healthcare providers and health facility surveys. Low- and middle-income countries (LMIC) such as Nigeria, Cameroon, Malawi, Zambia, India, Pakistan and Turkey calculate MMR applying health facility data [68-73].

Population census

More countries started applying population censuses for calculating maternal mortality indicators. According to the United Nations Principles and Recommendations for Population and Housing Censuses, the method envisions asking additional two questions during the census interviews about maternal deaths in a household during a defined interval of time [74]:

- Was the death due to an accident, violence, homicide or suicide?
- If the deceased was a woman aged 15–49, did the death occur while she was pregnant, during childbirth or during the six weeks after the end of pregnancy?

Following the UN issued recommendations, several countries added these questions to the regular census questions with aim to ascertain the maternal death (during pregnancy, childbirth or postpartum). The advantage of population census is cost-effectiveness. No additional costs are required, the data is obtained as part of regular country census. Yet, a census data could not be used for the routine data tracking given that it usually is conducted rarely, only once in every 10 years. The countries successfully applying population census for calculating mortality

indicators include but are not limited to: Latin America (Honduras, Nicaragua and Paraguay), South Africa, Burkina Faso, and Indonesia [75].

Population or household surveys

Population or household surveys are significant source of maternal mortality data in countries with absence or limited capacity of routine health information systems. The population or household surveys are conducted at the household level and gather information on maternal deaths events. The drawback of the method is that the surveys should target a relatively large sample size to get statistically significant results for the rare events that maternal deaths represent. The sample countries applying this method are Ethiopia, Kenya, Malawi, Senegal, Colombia, Sri Lanka, Indonesia, Jamaica [65].

Sisterhood methods

The sisterhood method is an indirect measurement technique frequently used for calculating maternal mortality ratios. In contrast with population surveys, the method does not require large sample sizes, as it gets information by interviewing respondents on the survival of all their adult sisters born to the same mother and there may be several sisters per household. The sisterhood methods can be either direct or indirect [76]. The direct method identifies any death that occurs during pregnancy, childbirth or the postpartum period; the indirect sisterhood approach identifies pregnancy-related deaths rather than true maternal deaths.

One of the limitation of this method is the likelihood for overestimating maternal mortality rates due to the inclusion of coincidental and sometimes non-maternal deaths. In contrast, the sisterhood method does not capture maternal deaths due to abortion. Another important limitation of the sisterhood method is that it calculates mortality related to the long period – 10-12 years for indirect and 6 years for direct method. As such the method is not useful for assessing a potential impact of a health intervention programs/initiatives [40].

Reproductive age mortality studies

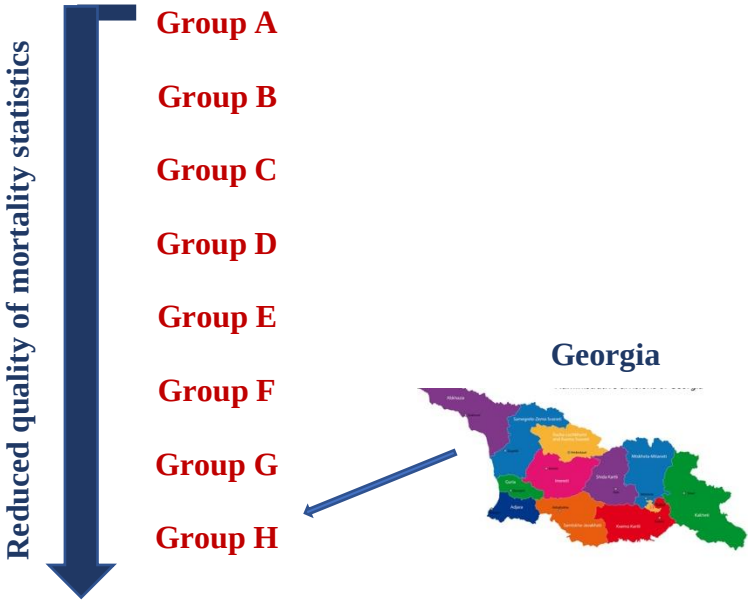
Reproductive Age Mortality Study (RAMOS) is widely acknowledged to be a gold standard for calculating MMR in countries with weak and immature birth and death registration systems. The effective and robust method applies both active and passive data collection tools. The method implies retrospective or prospective identification of all deaths cases of women of reproductive age by triangulations of different data sourced. Each death is evaluated individually using verbal autopsy and interview with household members, death certificate and medical record reviews and as such the method allows to differentiate maternal death cases from other causes of death. Hence, the method provides the most complete, accurate and contemporaneous estimate of MMR in settings with absence of advanced death registration system. Importantly, the method also allows to identify and code correctly the cause of maternal death, which represents an important advantage given the predominance of misclassification of ICD-10 coding and therefore problems in identification of true numbers of maternal deaths.

The methods applied by countries for calculating maternal mortality ratios varies substantially depending on the maturity of CRVS and health information systems. Even in countries with relatively good death registration systems, maternal deaths are underreported due to misclassification of the cause of death. Consequently, the level of underreporting of maternal deaths varies. The variation between countries in underreporting of maternal mortality ranges from 25% to 90% [77]**.**

Importantly, the WHO distinguishes eight group of countries (ranging from A to H) based on the quality and accuracy of maternal mortality statistics (*Figure 8*). Group A includes countries with the most advanced death registration and cause-of-death ascertainment systems. From Group A to Group H, the quality of mortality statistics declines in alphabetical order, with

Group H uniting countries with the weakest system to register and to correctly classify the cases of maternal death. Georgia used to belong to the latter category (Group H), due immature and suboptimal CRVS and health information systems, unable to calculate and provide reliable national estimates of MMR [78].

***Figure 8**: Country groupings by quality of mortality statistics*



Quality of mortality statistics in Georgia

After gaining independence in 1991, the Georgian health information system remained immature for over a decade, with questionable quality and completeness of data systems. Both maternal and perinatal birth and mortality statistics suffered from considerable margin of inaccuracy, inconsistency and underreporting, and significant discrepancies were present between different national data sources. Due to the immaturity of death and birth registration system, many of the death and birth cases were going unreported. For example, in 1998, 26.7% of infant deaths registered at hospitals were not registered by the Civil Registry Bureau. In the same year, six maternal deaths were documented by hospitals, but none of them were recorded

by the Civil Registry. Birth certificates were not issued for 22% of live births in maternity hospitals [79].

To address shortcomings of some aspects of the health information systems, specifically mortality statistics, the Ministry of Health (MoH) revised a format of the Medical Death Certificate and added the pregnancy check-box to the form in 2003. Yet, implemented interventions were not proved to be sufficient in addressing deficiencies of death and birth registration system. The completeness and accuracy of mortality statistics remained suboptimal.

For countries such as Georgia, where CRVS and health information systems lack both the ability to count all deaths and correctly classify the cause of death, the WHO estimates of maternal mortality are based on statistical modeling. However, that statistical model-based estimates often inaccurate for analyses of trends and tracking changes and the underlying assumptions these estimates are built upon are not country-specific [80].

Therefore, the country designed and carried out the first Reproductive Age Mortality Study (RAMOS08), with the aim to determine the true levels of maternal and reproductive age mortality of Georgian women in 2006 and to compare with officially reported data. The study was conducted with USAID support and jointly with the US Centers for Disease Control and Prevention (CDC), and the National Center for Diseases Control and Public Health (NCDC). Being the first of its kind in Eastern Europe, the study investigated the deaths of all Women of Reproductive Age (WRA) (15-49 years) who died in 2006. The findings were of critical policy importance in providing true level of maternal mortality and disclosing the extent of deficiencies in the official mortality statistics in Georgia. The study documented significant underreporting of maternal mortality (65% of all maternal deaths went unreported) and

substantial gaps in maternal death registration system [80]. Importantly, the study findings led to implementation of several important initiatives toward improving maternal death registration, health information system and vital statistics. In 2010, a civil registration reform introduced monetary penalty for failing to report death events [81-82]. In 2011, MoH initiated the transition from paper-based to electronic medical death certificates, which included underlying cause of death [83]. The Georgian Statistics Office began to match maternal death certificates to birth and fetal death certificates. The NCDC introduced active surveillance of maternal mortality by incorporating WRA death into an integrated electronic disease surveillance system (IEDSS) and implementing the verbal autopsy methodology to review all pregnancy-related deaths.

In 2013, the MoH adopted a national policy of mandatory notification of maternal death/stillbirth/0-5 years children's death [51]. The policy envisioned mandatory telephone notification to MoH within one hour of death identification, e-mail notification within 24 hours of death, and submission of relevant medical records to the Health Department of MoH within 5 days.

Implemented proactive measures were expected to improve significantly the quality of mortality statistics in Georgia, and thereby less gaps between official statistics and mortality estimates.

An important milestone was establishment of a real-time electronic maternal and child health management information system, the "Birth Registry", with support from the UNICEF and Norwegian technical experts. The registry launched in 2016 allows continuous monitoring of pregnant women from the first antenatal visit until childbirth and discharge from the hospital. The comprehensive system provides an ample information on wide array of indicators and

allows to track the quality of obstetric and neonatal services provision along with pregnancy outcomes, including maternal and perinatal/neonatal death. Yet, the accuracy and completeness of the birth registry data needs continuous monitoring and verification.

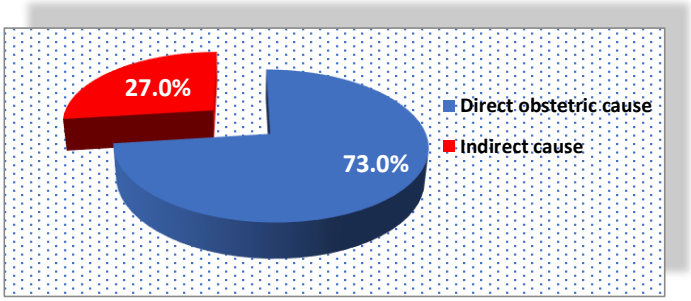
The second RAMOS designed and implemented in Georgia in 2014 aimed to obtain accurate measure of maternal mortality for 2012. The study timing was six years after the first RAMOS that produced, for the first time, the accurate maternal mortality figures. The current study is of paramount significance to obtain an accurate measure of maternal mortality and to understand the maternal mortality trend. Importantly, we assess whether policy changes and advances in death registration /notification systems lead to improvements in quality of mortality statistics and reduce the level of underreporting.

2.3 Causes of maternal death

Understanding the causes of maternal death is a key for averting preventable death through developing adequate policy and effective health-care solutions and health program decisions. Yet, accurate identification of causes of maternal death is challenging in many countries. This is due to inadequate data collection and absence or dysfunctional death registration systems, which is a substantial source of misclassification and/or misinterpretation of cause of death coding rules, and inadequate cause of death ascertainment practices.

In 2014, WHO performed a systematic review, developed and analyzed estimates of the causes of maternal death at a global, regional, and sub-regional levels [7]. According to the findings of this global review, the direct obstetric causes were the leading reasons of all maternal deaths between 2003 and 2009 and accounted for as much as 73% of all deaths and remaining 27% of deaths were due to indirect causes (*Figure 9*).

***Figure 9**: Global maternal death causes: direct vs indirect*

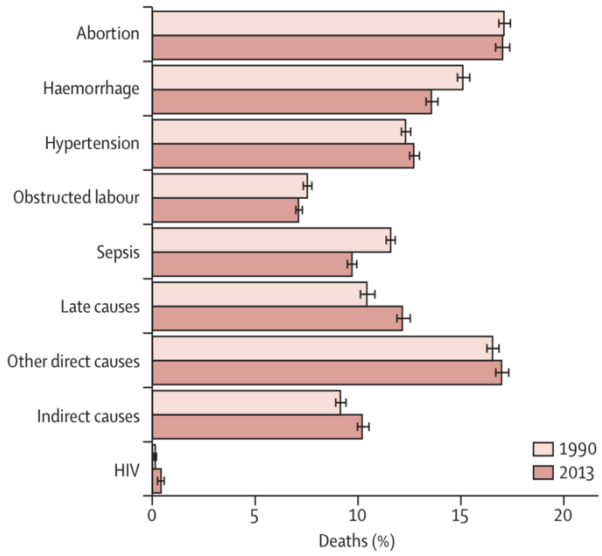


At the global level, hemorrhage was a dominant direct cause of maternal death, accounting for 27.1% of all deaths, followed by hypertensive disorders with 14.0%, sepsis 10.7 %, abortion 7.9 % and embolism 3.2%. The remaining deaths (9.6%) were due to other direct causes.

The breakdown of indirect causes of maternal deaths showed that as much as 70% are due to preexisting clinical conditions. HIV was responsible for 5.5% of all maternal deaths globally [7]. As expected, the share of maternal deaths due to HIV/AIDS was lower in developed regions in comparison with the developing world (2.5% and 5.5% respectively).

The distribution of causes of maternal death changed slightly with time. The share of indirect causes increased from 1990 to 2013 as documented by a systematic analysis for the Global Burden of Disease Study [84] (*Figure 10).*

***Figure 10**: Global maternal death causes trend, 1990 vs 2013*



The trend showed an overall reduction of the relative rates of hemorrhage and sepsis, while an increase was documented for other direct causes, late maternal death and hypertension.

The distribution of the causes of maternal death varies substantially across the regions and between developed vs developing world. Indirect cause is the leading cause in developed countries, accounting for 24.7% of maternal deaths with the second leading cause being hemorrhage (16.3%). Among the indirect maternal deaths, non-communicable diseases such as cardiovascular, anemia, neoplasms and diabetes are the commonest reported causes of death globally. In the developing part of the world, both indirect causes and hemorrhage have similar shares of all maternal causes (27.5 and 27.1% respectively) [7] (*Figure 11*).

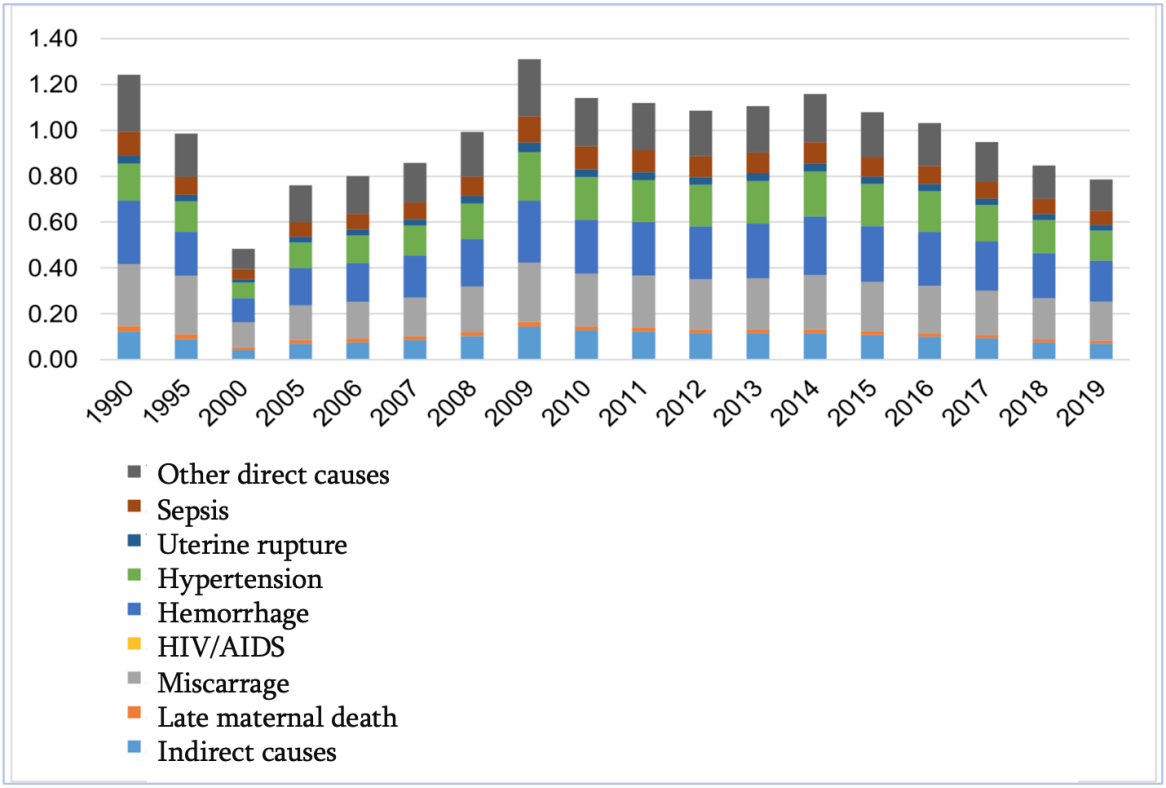
***Figure 11**: Distribution of causes of maternal death by MDG regions*

	Abortion		Embolism		Haemorrhage		Hypertension		Sepsis		Other direct causes		Indirect causes	
	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)	N	% (95% UI)
Worldwide	193 000	7·9% (4·7–13·2)	78 000	3·2% (1·8–5·5)	661 000	27·1% (19·9–36·2)	343 000	14·0% (11·1–17·4)	261 000	10·7% (5·9–18·6)	235 000	9·6% (6·5–14·3)	672 000	27·5% (19·7–37·5)
Developed regions	1100	7·5% (5·7–11·6)	2000	13·8% (10·1–22·0)	2400	16·3 (11·1–24·6)	1900	12·9% (10·0–16·8)	690	4·7% (2·4–11·1)	2900	20·0% (16·6–27·5)	3600	24·7% (19·5–33·9)
Developing regions	192 000	7·9% (4·7–13·2)	76 000	3·1% (1·7–5·4)	659 000	27·1% (19·9–36·4)	341 000	14·0% (11·1–17·4)	260 000	10·7% (5·9–18·7)	232 000	9·6% (6·4–14·3)	668 000	27·5% (19·7–37·6)
Northern Africa	490	2·2% (0·9–4·9)	720	3·2% (0·9–8·9)	8300	36·9% (24·1–51·6)	3800	16·9% (11·9–22·9)	1300	5·8% (2·3–12·9)	3800	17·1% (7·7–30·8)	4000	18·0% (9·5–30·2)
Sub-Saharan Africa	125 000	9·6% (5·1–17·2)	27 000	2·1% (0·8–4·5)	321 000	24·5% (16·9–34·1)	209 000	16·0% (11·7–21)	134 000	10·3% (5·5–18·5)	119 000	9·0% (5·1–15·7)	375 000	28·6% (19·9–40·3)
Eastern Asia	420	0·8% (0·2–2·0)	6500	11·5% (1·6–40·6)	20 000	35·8% (10·9–68·2)	5900	10·4% (3·9–20·2)	1500	2·6% (0·4–9·7)	8000	14·1% (2·0–51·3)	14 000	24·9% (6·4–58·8)
Southern Asia	47 000	5·9% (1·5–17·3)	17 000	2·2% (0·5–6·8)	238 000	30·3% (14·0–54·8)	80 000	10·3% (5·8–16·6)	107 000	13·7% (3·3–35·9)	65 000	8·3% (3·3–17·7)	229 000	29·3% (12·2–55·1)
Southeastern Asia	11 000	7·4% (2·8–18·4)	18 000	12·1% (3·2–33·4)	44 000	29·9% (15·2–51·3)	21 000	14·5% (8·4–22·7)	8100	5·5% (1·8–15·0)	20 000	13·8% (5·6–31·2)	25 000	16·8% (7·8–34·2)
Western Asia	860	3·0% (1·0–7·6)	2600	9·2% (3·3–22·6)	8900	30·7% (17·4–49·1)	3900	13·4% (7·5–21·2)	1400	4·8% (1·5–13·1)	4500	15·6% (6·6–33·7)	6700	23·4% (11·3–43·1)
Caucasus and central Asia	250	4·6% (2·7–8·2)	590	10·9% (6·2–18·2)	1200	22·8% (17·2–30·3)	790	14·7% (11·6–18·3)	460	8·5% (5·7–13·6)	910	16·8% (12·6–23·2)	1200	21·8% (16·2–29·9)
Latin America and Caribbean	6900	9·9% (8·1–13·0)	2300	3·2% (2·6–4·7)	16 000	23·1% (19·7–27·8)	15 000	22·1% (19·9–24·6)	5800	8·3% (5·6–12·5)	10 000	14·8% (11·7–19·4)	13 000	18·5% (15·6–22·6)
Oceania	290	7·1% (1·2–22·9)	610	14·8% (1·9–47·6)	1200	29·5% (8·5–61·7)	560	13·8% (4·9–25·8)	200	5·0% (0·6–18·5)	510	12·4% (2·3–38·7)	710	17·4% (4·7–44·3)

Data shown are the estimated proportion of cause of death (%) with 95% uncertainty interval (95% UI).

According to the MDG regional grouping, Georgia belongs to the "Caucasus and central Asia" group, where hemorrhage is the leading cause among the maternal death causes (22.8%), followed by indirect causes (21.8%). Georgian official statistics also provide data on causes of maternal death per year, where hemorrhage and hypertension are dominant causes of death [25] (*Figure 12*). Yet, the data need to be interpreted with caution, especially for previous decades, due to the poor registration and cause of death ascertainment systems.

***Figure 12**: Causes of maternal death, Georgia (1990-2019)*



The present study is the second (after RAMOS08) in attempting to identify true causes of maternal death in Georgia. This is of critical importance for getting evidence-based understanding of causes of death and conditions leading to maternal death, and for developing and implementing effective policy solutions and health program decisions. Our study also identified timing of maternal death, which complements the cause of death information and facilitates rational planning and implementing maternal health programs, priority setting and allocating relevant resources.

2.4 Quality of care and factors for substandard quality

High quality of care is a critical factor in eradicating preventable maternal deaths and a significant challenge in many countries, including developed. As shown by the confidential enquiries, substandard and poor-quality care is the leading factor in two-thirds of maternal deaths in European countries [85].

Quality of care is a complex concept, determined by multiple factors and having various dimensions. According to the U.S. Institute of Medicine report "Crossing the Quality Chasm: A New Health System for the 21st Century" [86], the quality care should be:

- **Safe**—providing health services which minimizes risks and harm to patients, avoids preventable injuries and medical errors
- **Effective**—providing services which are based on the current scientific evidence
- **Patient-centered**—providing care that is respectful and that takes into account the preferences, needs, and values of each service user
- **Timely**—minimizing delays in providing and receiving health care
- **Efficient**—providing care in a way that maximizes resource use and minimizes waste
- **Equitable**—delivering care that is of the same quality, not depending on the race, ethnicity, religious, geographic location and socioeconomic status.

The multiple factors influencing the quality are interconnected. They include the availability of infrastructure and supplies, the health care personnel's level of training, the preparedness of facilities to provide required level of specialized care when complications arise, referral system, provider-patient relationships, as well as leadership, governance and accountability for quality. There is close relationship between quality of care and domains of the health systems building blocks and therefore, assessment of quality of care and health system performance often based on common frameworks. It is worth to mention that in conceptualizing the quality of care "evidence" generation and its increased availability, Cochrane collaboration plays an important role.

In low- and middle-income countries, maternal mortality reduction is slow due to the limited quality of provided services, and lack of the health systems' capacity to timely identify and adequately manage pregnancy complications [87].

Monitoring and clinical auditing of individual maternal deaths, both early and late, provide insight into different aspects of the quality of health services, and help to define the elements of delay and substandard care. These are central for detecting gaps in the health system and recommending policies and improvements to health care decision makers. As such, maternal and perinatal death audit and review is widely acknowledged and recommended as a high-impact intervention to improve quality of service provision, reduce maternal mortality, and a key to accomplishing the SDGs.

The maternal death audit methodology was proposed by the WHO in 2004, in the publication Beyond the Numbers (BTN). In BTN the WHO defines maternal death review as a "qualitative, in-depth investigation of the causes of, and circumstances surrounding, maternal deaths". The publication describes several methodologies for the audit [88] (*Table 7*).

***Table** 7: Audit methods*

Name	Operational definition	Prerequisites
Community-based maternal death reviews (verbal autopsies)	A method of finding out the medical causes of death and ascertaining the personal, family or community factors that may have contributed to the deaths in women who died outside of a medical facility.	Requires co-operation from the family of the woman who died, and sensitivity is needed in discussing the circumstances of the death.
Facility-based maternal deaths review	A qualitative, in-depth investigation of the causes of and circumstances surrounding maternal deaths occurring at health facilities. Deaths are initially identified at the facility level, but such reviews are also concerned with identifying the combination of factors at the facility and in the community that contributed to the death, and which ones were avoidable.	Requires co-operation from those who provided care to the woman who died, and their willingness to report accurately on the management of the case.
Confidential enquiries into maternal deaths	A systematic multi-disciplinary anonymous investigation of all or a representative sample of maternal deaths occurring at an area, regional (state) or national level. It identifies the numbers, causes and avoidable or remediable factors associated with them.	Requires existence of either a functioning statistical infrastructure (vital records, statistical analysis of births and deaths, human resources, recording clerks, etc.) or nominated professionals in each facility to regularly report maternal deaths to the enquiry.
Surveys of severe morbidity (near misses)	The identification and assessment of cases in which pregnant women survive obstetric complications. There is no universally applicable definition for such cases and it is important that the definition used in any survey be appropriate to local circumstances to enable local improvements in maternal care.	Requires a good-quality medical record system, a management culture where life-threatening events can be discussed freely without fear of blame, and a commitment from management and clinical staff to act upon findings.
Clinical audit	Clinical audit is a quality-improvement process that seeks to improve patient	It must be possible to identify relevant cases

	care and outcomes through systematic review of aspects of the structure, processes, and outcomes of care against explicit criteria and the subsequent implementation of change. Where indicated, changes are implemented at an individual, team or service level and further monitoring is used to confirm improvement in health care delivery.	from facility registers and retrieve the case notes. Health care personnel must feel able to openly discuss case management and be willing to envisage the application of revised protocols for care.

Since the publication of BTN, maternal death reviews have been widely accepted in many developed countries, however, the extent and experience of death audits remains relatively limited in the developing world [89-90].

The scope of maternal death audit varies from a simple case description to a systematic in-depth analysis of the causes of substandard care accepted in many developed countries. In-depth analyses frequently apply a three delays model – a conceptual framework of three phases of delays which identifies factors impeding the decision to seek obstetric services and highlighting specific barriers and challenges in provision and utilization of quality and timely obstetric care [91-92]. It is estimated that 50-70% of maternal deaths can be prevented simply if the woman gets access to appropriate and good quality care [85].

Factors preventing women from receiving appropriate medical care were grouped by chronological order into **Three Phases of Delay** [92] **(***Figure 13)***:**

Phase I

The delay in deciding to seek care is determined by one or multiple factors - barriers/ constrains to the utilization of health care service delivery, which most commonly includes distance, financial issues, sociocultural factors (i.e. women's status determined by the educational, cultural, financial, social and political position of a women in a specific community), recognition of need to seek care (individuals' assessment of a health condition) and perceived quality of care. Major actors in decision to seek care include individual, spouse, family, relative, friend.

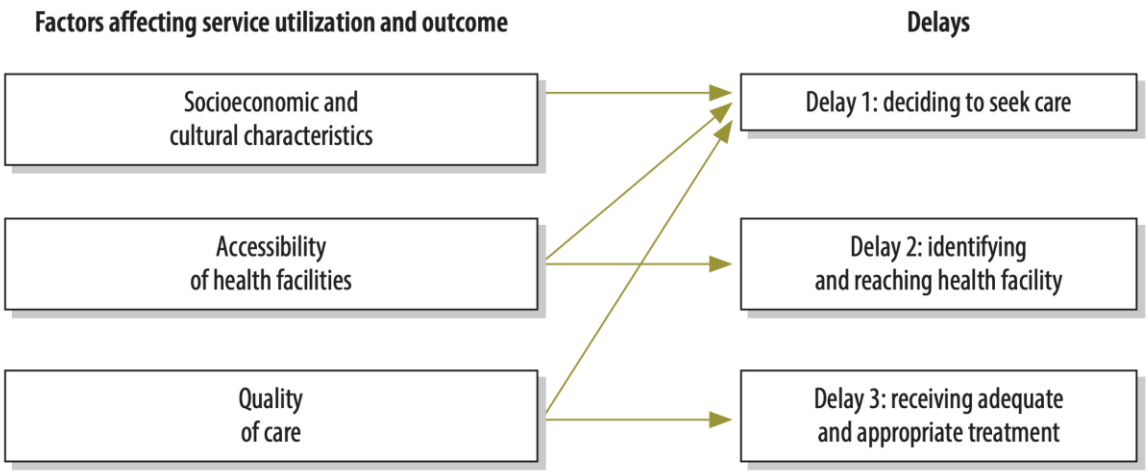
Phase II

The delay in reaching medical facility is determined commonly by the accessibility of services, which plays a double role in the health-care-seeking behaviors, affecting both the phase I and a phase II of the delay. The factors that affect timely reaching of the medical facility includes location of health care facilities, the travel distance to the clinics, availability and cost of transportation, physical condition of the roads etc. The delay in accessing medical facility is very common among three delays. It is specifically frequent among rural populations, where access to health care services is complicated.

Phase III

The delay in receiving adequate care includes adequacy of the referral system; shortages of essential supplies, drugs, blood, equipment, competence and availability of personnel; and competence of available personnel. Late or wrong diagnosis, recognition of complications, and inadequate response by the personnel are also factors that play a role in receiving timely and appropriate care.

***Figure 13**: The three-delay model in emergency care*



Importantly, maternal death may be an outcome of combination of two or all three phases of the delay, yet any one phase can also lead to the fatal outcome, if not quickly and properly addressed.

The present study is of high scientific and policy importance since for the first time it provided in-depth analyses of each maternal death, identified main causes of deaths and contributing factors. We assessed the elements of substandard medical care, including timely identification of risk or complications, adequate referral to the appropriate level obstetric facility, evidence-based management of a severe maternal condition, and timely intervention. Importantly, the study also addressed the late maternal deaths, contributing to the knowledge around these deaths.

3. RESEARCH QUESTIONS AND OBJECTIVES

This thesis has the following research questions and objectives:

3.1 Research questions

- What is a mortality pattern and trend among women of reproductive age in Georgia? (Study I)
- What is maternal mortality incidence, causes and underreporting in 2012 and how it changed from 2006 to 2012? (Study II)
- What are the underlying causes of maternal death, suboptimal factors in care contributing to the maternal fatal outcome? (Study III)

3.2 Research objectives

- Provide an understanding of a mortality pattern and trend among women of reproductive age in Georgia and how maternal mortality features in the overall mortality burden of women of reproductive age (Study I);
- Provide accurate data on maternal mortality ratio in Georgia for 2012 (Study II);
- Understand the level of underreporting of maternal deaths in Georgia in 2012 (Study II);
- Investigate the leading causes of maternal death and changes in the causes of maternal death from 2006 to 2012 (Study II);
- Analyze the underlying causes of maternal death and suboptimal factors in care contributing to the maternal fatal outcome (Study III).

4. METHODOLOGY

Reducing maternal mortality and improving maternal health cannot be accomplished without accurate knowledge on mortality statistics, causes of maternal death, quality of care provided and potential gaps in the health system which contribute to poor outcomes.

Georgia long belonged to the category of countries with immature, weak civil registration systems, with narrow capacity to count and correctly classify the causes of maternal death. The Reproductive Age Mortality Study (RAMOS) conducted in Georgia in 2008 provided the first accurate estimates of maternal mortality data for 2006 and documented a dramatic gap between maternal mortality ratios by official statistics and study findings: 23 vs. 44 per 100 000 live births, respectively. Six years after RAMOS08, the second nationwide RAMOS14 was carried out in Georgia. The aim was to get insight into the deaths of women of reproductive age, to obtain an accurate maternal mortality data and to assess extent of improvements in mortality statistics in the country as a result of wide array of measures implemented for strengthening civil registration system.

The second RAMOS was conducted in 2014 by the National Center for Disease Control and Public Health (NCDC&PH), using retrospective 2012 data and replicating the methodology of the RAMOS08.

Ethical approval

The study protocol was approved by the Georgian Institutional Review Boards of NCDC & PH (IRB 2017- 035 and 2019-013) and the Regional Committee for Medical and Health Research Ethics, South East Norway (2015/1352 REK). Written informed consent was obtained from all respondents (family members or caretakers of the deceased women) prior to the interviews.

4.1 Key definitions

The study applied the definition of maternal death and underlying causes of death classification from the WHO application of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD – 10) to the deaths during pregnancy, childbirth and puerperium: ICD-MM [93].

Maternal death

A maternal death is 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.

Late maternal death

A late maternal death is the death of a woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.

Direct obstetric death

Direct obstetric deaths are those resulting from obstetric complications of the pregnancy state (pregnancy, labour and the puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.

Indirect obstetric death

Indirect obstetric deaths are those resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy.

Coincidental death

Coincidental deaths are those deaths that occur during pregnancy, childbirth or the puerperium (42 days) but that are not by definition considered maternal deaths.

Underlying cause of death

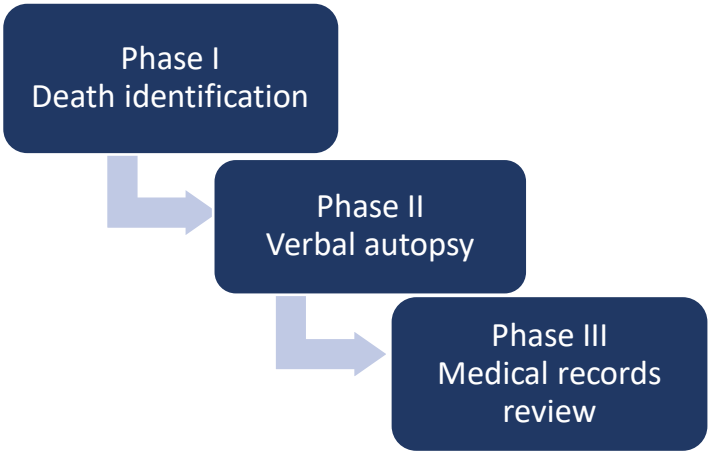
Underlying cause of death is defined as the disease or condition that initiated the morbid chain of events leading to death or the circumstances of the accident or violence that produced a fatal injury.

4.2 Study target population and data collection

The target population for the study included all women aged 15 to 49 with a permanent residence in Georgia, who died in 2012. The year 2012 was selected as the most recent year for which full and error-checked databases were available at the initiation of the study.

The research methodology involved investigation of all causes of death to women of reproductive age (WRA). There were three phases of data collection: death identification, personal interviews with relatives of deceased women using a verbal autopsy (VA) questionnaire and medical record review at the last health facility that provided care for the woman during her fatal condition in pregnancy or 1 year after childbirth (*Figure 14)*. The data collection was conducted in 2014-2015.

***Figure 14**: Data collection phases*



Phase I: Identifying all deaths among women of reproductive age

Phase I envisioned identification of all potentially eligible deaths that occurred among reproductive age female permanent residents of Georgia through triangulation of the multiple data sources:

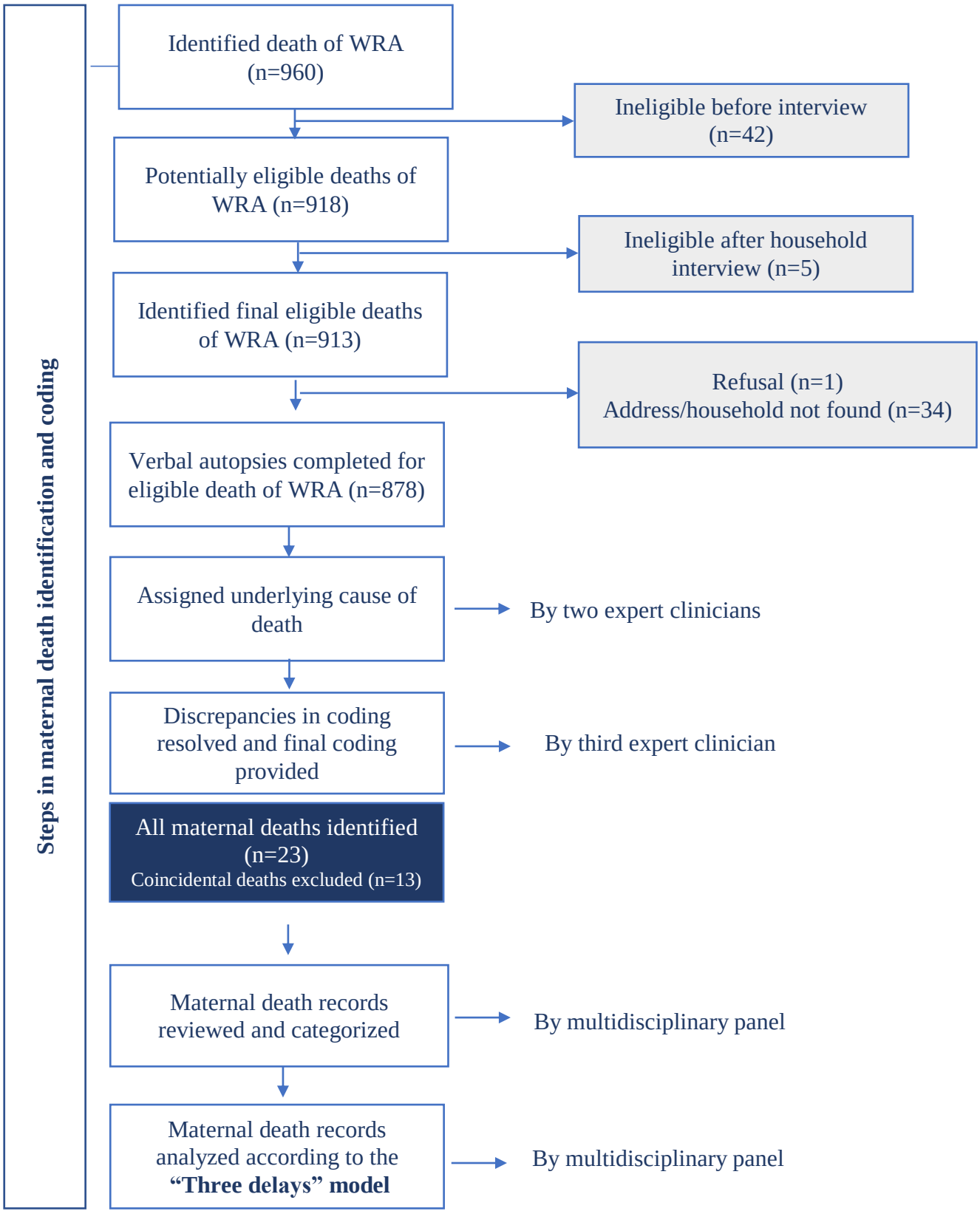
- Civil registration vital statistics mortality electronic dataset
- Routine health statistics and surveillance data from the NCDC&PH
- Hospital and ambulance service registers' electronic datasets
- Regional death registers
- Community informants contacted during the field investigation.

In total, 960 potentially eligible deaths in WRA in 2012 were identified through triangulation of different data sources, out of which 42 were ranked as ineligible before and 5 after the household interviews, yielding to final eligible 913 deaths to WRA (*Figure 15*).

Phase II: Investigating all deaths among women of reproductive age through verbal autopsies

In the second phase, the VA interviews with family members or other caregivers of decedents were conducted by household visits within 24 months of death, considering the local cultural context for the mourning period. VAs was successfully completed for 878 deaths, which yielded a response rate of 96.2%. Only one family refused to be interviewed, and 34 families could not be traced after their family member's death.

***Figure 15**: Case identification of study eligible maternal deaths*



Detailed information on premortem illness signs and symptoms was collected by skilled female interviewers with a medical background using the VA instrument. This instrument was developed for the RAMOS08 and was based on the questionnaires used in pregnancy mortality studies and surveillance systems conducted by the Centers for Diseases Control (CDC) in the United States and Latin America combined with elements from the WHO international standard VA questionnaire [80, 94]. A comprehensive history of use of health- care services prior to death had been added to capture barriers to appropriate and timely care and to facilitate needed improvements in the health system.

Completed VA questionnaires were reviewed blindly by two expert clinicians approved by the Ministry of Labor, Health and Social Affairs. They assigned the most probable underlying cause to each death according to the rules of the International Classification of Diseases, 10th revision (ICD-10) [95]. Discrepancies in coding were resolved by a third physician who adjudicated the final diagnosis.

Phase III: Medical records reviews

During the third phase, the medical records were reviewed for VA-derived cases for all women who died during pregnancy, childbirth or within one year after childbirth based on the ICD for Maternal Mortality (ICD-MM) definitions ("direct", "indirect", and "late" maternal deaths). There were totally 36 cases identified as pregnancy related deaths. The review was done at the health care facility last visited by the deceased. Interviews were conducted with health professionals for additional details on the chain of clinical events leading to the death as well as treatment specifics.

Reviews identified 13 deaths as co-incidental. For 23 deaths categorized as maternal, panel of experts conducted additional in-depth review of treatment courses and care provided and analyzed preventability of maternal death. Data were analyzed according to the "three delays"

model: identifying potential “delay in the decision to seek care”, “delay in arrival at a health care facility”, and “delay in the provision of adequate care”.

We considered existing Georgian national guidelines and clinical protocols as the reference standard of care for evaluating timely recognition and treatment, appropriate management and referral. Where these were lacking, we applied guidelines from the Royal College of Obstetricians and Gynecologists (RCOG) [96-97], American College of Obstetricians and Gynecologists (ACOG) [98], and the WHO [99-101].

Categorization of the quality of care was made based on the United Kingdom’s scoring system [11] as follows: 1 - good care, 2 - improvements to care which would have made no difference to the outcome, and 3 - improvements to care which would have made a difference to the outcome. All cases of maternal death were finally revised and discussed with a panel of national expert-physicians for a conclusive consensus decision on the cause of maternal death.

4.3 Variables and measurement

The key socio-demographic and pregnancy history variables derived from the previous studies were assessed for investigating causes of maternal death. Categorical predictor variables included age, mode of delivery and timing of death.

The continuous variable age was categorized in four groups according to the commonly applied delivery-related age categorization:

- <21
- 21-30
- 31-40
- >40

The variable “delivery mode” was standardly categorized as:

- Miscarriage/ectopic pregnancy
- Induced abortion

- Vaginal delivery
- Caesarean delivery
- Undelivered/pregnant

Similarly, the standard categorization was applied for describing the timing of maternal death:

- Antepartum
- Postpartum
- Post-abortion

The outcome variable causes of maternal death was grouped according to the ICD-MM - the WHO Application of ICD-10 classification of deaths during pregnancy, childbirth and the puerperium. The aggregated groups were "clinically and epidemiologically relevant, mutually exclusive and totally inclusive and descriptive of all causes of maternal and pregnancy-related deaths" [93].

4.4 Statistical analyses

In all studies the descriptive statistical analyses were performed applying SPSS version 21.0 (IBM, Armonk, NY, USA). We did univariate, stratified calculations, constructed frequency tables and performed cross tabulation to investigate pattern of maternal mortality in Georgia. The overall MMR was calculated as number of all maternal deaths per 100 000 live births. Additionally, patterns of misclassification between CRVS, VA diagnoses and multidisciplinary panel of medical experts were also analyzed by cross-tabulating of the data.

Agreement of cause attribution between the VA and CRVS system was assessed based on the Cohen's kappa (k) statistic, with the corresponding 95% CIs. Percent agreement (number of agreement values / total values) was initially used to determine interrater reliability. Yet, to avoid the "chance agreement" between the sources, the Cohen's kappa (k) statistic was applied, which considers the element of chance. The strength of agreement according to the Kappa

statistic ranged from 0 to 1 and is categorized in the following way [102]: 0 - agreement equivalent to chance, 0.01 – 0.20 - poor agreement, 0.21 – 0.40 - fair agreement, 0.41 – 0.60 - moderate agreement, 0.61 – 0.80 - good agreement, 0.81 – 0.99 - near perfect agreement, 1 - perfect agreement.

The sensitivity and positive predictive values (PPV) of the CRVS system for each cause category were measured against VA diagnosis as a reference standard. The Diagnostic and Agreement Statistic (DAG_Stat) spreadsheet was applied to compute estimates of kappa, sensitivity, and PPV with the corresponding 95% CIs for measuring interrater agreement. The misclassification pattern of diagnoses between CRVS and VA were analyzed by cross-tabulating these two data based on the shortened WHO list.

VA-based causes of death for all women of reproductive age were reclassified, based on Global Burden of Disease (GBD) classification, into three broad categories: communicable, maternal, neonatal, and nutritional disorders; NCDs; and injuries. The fourth category - undetermined causes of death combined all deaths assigned ill-defined and unknown codes.

Crude mortality rates (all-cause-, age- and cause-specific per 100 000 women) for all death of reproductive age women, including maternal death were calculated using the 5-year age group categories and the corresponding mid-year female population estimates as denominators obtained from the official sources [103].

Age-standardized death rates (ASDRs) were then computed for each women of reproductive age death category, including maternal death by applying age-specific death rates to the world standard population age distribution (2000–2025) using the direct method [104] and compared to those for the reference period of 2006. The ranking of death categories was also performed and compared to the death category ranking for 2006.

5. RESULTS

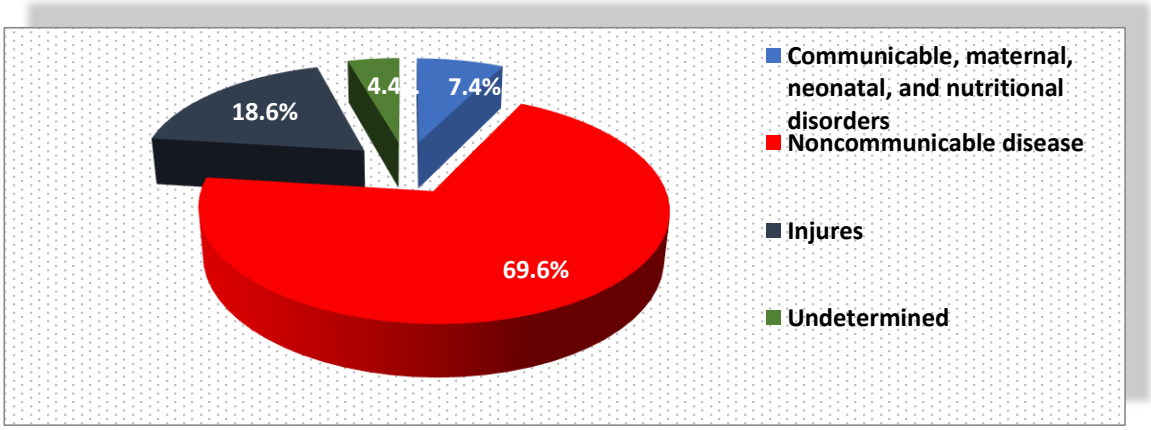
5.1 Paper I: Leading causes of death among women of reproductive age and burden of maternal disorders in the overall mortality structure of women of reproductive age in Georgia

Broad causes of death

After grouping the underlying cause of death based on the GBD classification, NCDs were by far the leading cause of death among the four broad categories of death, accounting for over two-thirds of all deaths (69.6%) or 53.1 deaths per 100 000 (*Figure 16*).

Cancer was the most common cause of death for women 15–49 accounting for 45.2% of all deaths or 34.5 per 100 000 followed by (13.2%). The external causes were the second-most common underlying cause of death (18.6%). This category was followed by communicable, maternal, neonatal, and nutritional disorders at 7.4% or 5.6 deaths per 100 000. Undetermined causes contributed to only 4.4% (Table 3, Paper1).

***Figure 16**: Causes of death of women of reproductive age (broad categories), Georgia RAMOS14*



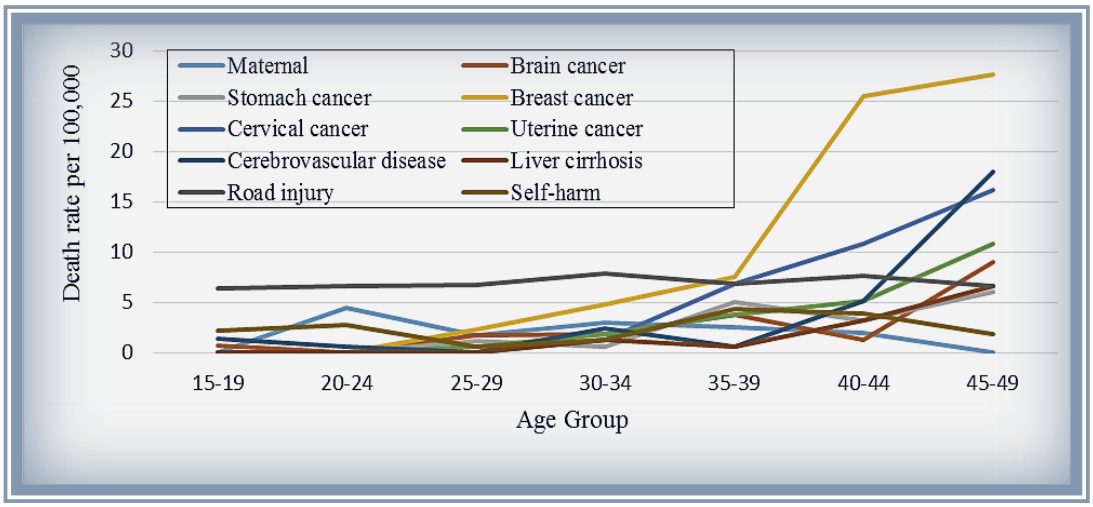
Specific causes of death

Based on the GBD classification (Table 3, Paper 1), breast cancer appeared to be the number one cause in women of reproductive age (15-49 years), accounting for 12.5% of all deaths or 9.6 per 100 000. Road injuries at 9.1% or 6.9 per 100 000 was the second followed by cervical cancer at 6.5% or 4.9 per 100 000. Cerebrovascular diseases were the fourth major cause (5.2%), whereas uterine cancer was the fifth (4.1%). Maternal disorders were the ninth leading causes of death at 2.6% or 2.0 per 100 000.

An analysis of specific causes of death by age categories identified road injuries as the principal cause of death in women aged < 35 years, killing nearly one-third (30.0%) of adolescent girls aged 15–19 years (Table 4, paper 1). In the same age category, <35 years, maternal disorders were the second most common cause of death, followed by breast cancer and tuberculosis (TB). Breast cancer was the principal cause in the older age groups (35-49 years), followed by cervical cancer and road injuries in those aged 35-44 years.

There is an observed sharp increase with age in mortality rates for all five cancer-related deaths, cerebrovascular diseases, and liver cirrhosis, as opposed to mortality rates for road injuries, suicide, and maternal disorders, remaining relatively stable or decreasing with age *(Figure 17*).

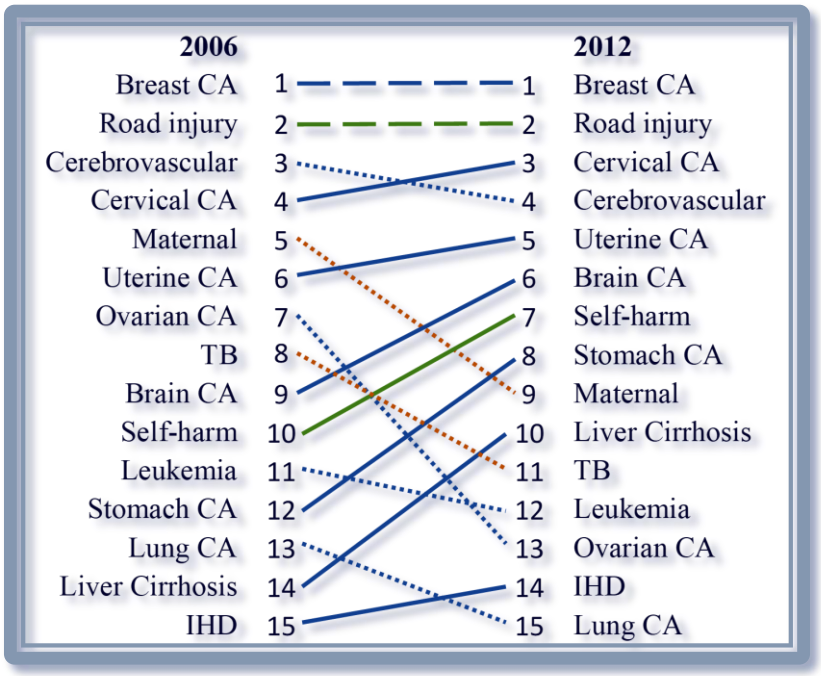
***Figure 17**: Cause-specific death rates by specific cause category and age group for women of reproductive age, Georgia RAMOS14*



Comparison of the leading causes of death in 2006 and 2012

A comparison of mortality estimates for the leading causes of death of Georgian women of reproductive age between 2006 and 2012, based on the two national RAMOS (RAMOS08 and RAMOS14) findings show that all-cause ASDR per 100 000 women was 70.0 in 2012, no statistically significant difference from 71.2 in 2006 (SRR 0.98; 95% CI 0.90-1.08, $p<0.05$). No statistically significant changes have been identified during that period in ASDRs for the broad categories of death, including NCD broad subgroups, except for a statistically significant decline (SRR 0.60; 95% CI 0.40-0.90, $p<0.05$) seen in undetermined causes, making them rank down to the fourth place compared to 2006 (Table 3, Paper 1).

***Figure 18**: Leading specific causes of death in women of reproductive age who died in 2006 and 2012. Georgia RAMOS08 and RAMOS14*



Abbreviations: CA, cancer; IHD, ischemic heart disease; TB, tuberculosis.

Among the major specific causes of death, statistically significant difference in the ASDR between comparison years was identified only for ovarian cancer, which more than halved (SRR 0.46; 95% CI 0.25-0.85, $p<0.05$) compared to 2006 (Table 3, Paper 1). Changes during that period were observed in both composition and rankings of the 10 leading specific causes of death, with only breast cancer and subsequent road injuries maintaining their dominant positions. Rank decrease was observed for maternal disorders, from fifths to ninth place. (Figure 18).

Cause agreement and misclassification patterns

The overall level of agreement on cause-of-death ascertainment between the CRVS and VA sources based on the WHO shortened list was fair (k=0.36; 95% CI 0.33-0.40), showing a slight improvement from that when using the WHO list (k=0.34; 95% CI 0.31-0.38). Individual

agreement was extremely poor for ill-defined causes and unspecified external causes, with the lowest kappa scores (0.04 and 0.06, respectively). Among specific causes of death, disagreement between the two sources was particularly evident for suicide, transport accidents, neurologic disorders, and liver diseases (k=0.12–0.20). By contrast, the level of agreement was good for respiratory TB, breast cancer, leukemia, malignant skin melanoma, brain cancer, and maternal causes (k=0.63-0.75), and almost perfect (k=0.81) for stomach cancer (Table 1, Paper 1).

The observed sensitivity of the CRVS system relative to the VA in identifying the major specific causes of death was largely unsatisfactory (<50%), with the lowest values for suicide, transport accidents, liver diseases, neurologic disorders, uterine cancer, and diabetes (Table 1, Paper 1). Sensitivity was higher (>60%) for maternal causes and ovarian cancer, and the highest for stomach cancer (76.9%). The PPVs of the CRVS system, ranging from 5.4% to 100%, were among the lowest for liver disease, diabetes, and IHD, while being the highest (100%) for transport accidents, brain cancer, maternal causes, and assault (Table 1, Paper 1).

The estimated degrees of over- and underdiagnosing for each cause category in CRVS due to misclassification are presented in Table 1, Paper 1. Percentage changes for most of selected causes of death were statistically significant (p<0.05), with the largest differences seen for transport accidents, suicide, and uterine cancer compared to other specific causes.

The details of the misclassification patterns for the major causes of death using the shortened WHO list are presented in Table 2, Paper 1. Most of deaths (214/229), ascertained by the CRVS system as ill-defined causes, were reclassified by the VA into a wide range of ICD cause categories. This was particularly evident for breast cancer (33/110), transport accidents (13/82), cervical cancer (15/57), cerebrovascular diseases (11/46), uterine cancer (11/36) and suicide

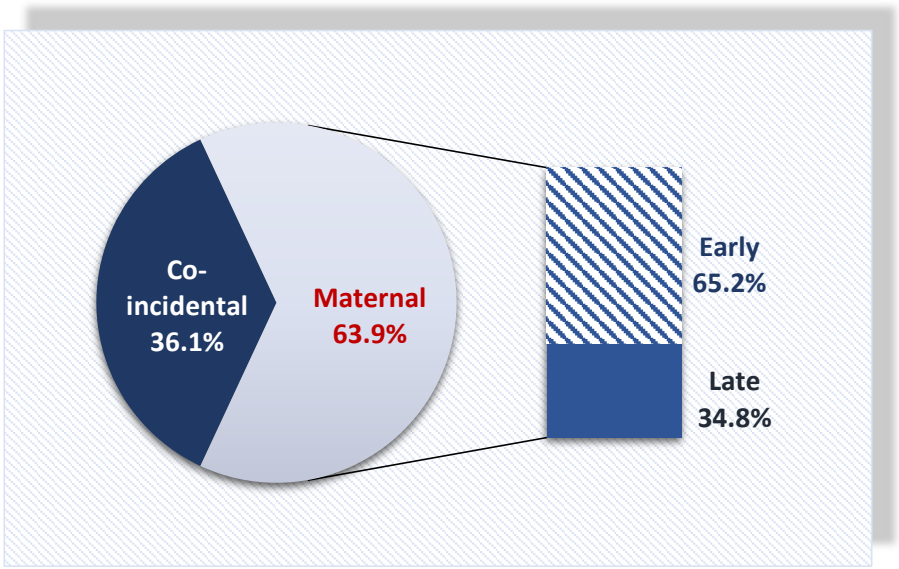
(7/27), as well as brain cancer (5/30) and maternal causes (5/23). Further increases in these important causes, namely breast cancer (16/110), cervical cancer (18/57), uterine cancer (17/36), cerebrovascular diseases (15/46), and brain cancer (9/30), as well as maternal causes (4/23) and suicide (4/27), were observed after their reallocation from various specific or unspecified causes of death of CRVS data.

5.2 Study II: Maternal Mortality in Georgia: Incidence, Causes and Level of Underreporting: A National Reproductive Age Mortality Study 2014

Characteristics of the Maternal Death Study Population

A total of 36 pregnancy-related deaths were identified. Among these, 23 (63.9 %) deaths were classified as maternal, directly or indirectly caused by pregnancy and 13 (36.1%) as deaths from co-incidental causes. Of the 23 maternal deaths, 15 (65.2%) were early and eight (34.8%) were late (*Figure 19*).

***Figure 19**: Classification of pregnancy related deaths, Georgia RAMOS14*



Of the 23 maternal deaths, about half of the women were 20-29 years of age at the time of death; 39% were 30-39 years; and 13 % were 40 years or older. We found the highest age-specific maternal mortality ratio in the older age groups (35-39 and 40-44), and the lowest in age group (25-29) (Table 1, Paper 2).

Pregnancy outcomes

Among the 23 maternal deaths, 52.2% (n=12) followed delivery of a live birth and 8.7% (n=2) occurred after a stillbirth, while 13%, (n=3) were still pregnant at the time of death. 17.4% women (n=4) died after early fetal loss (3 miscarriages, one ectopic pregnancy) and two after induced abortion (Table 2, Paper 2).

Causes of deaths

Direct obstetric deaths constituted 73.9% (n=17) of all maternal deaths. The four leading causes were sepsis, hemorrhage, pulmonary embolism and preeclampsia/eclampsia (Table 3, Paper 2).

Other direct causes of deaths were sudden death (n=1), unanticipated complication of anesthesia during delivery (n=1) and complication following intrauterine fetal death (IUFD) at term (n=1).

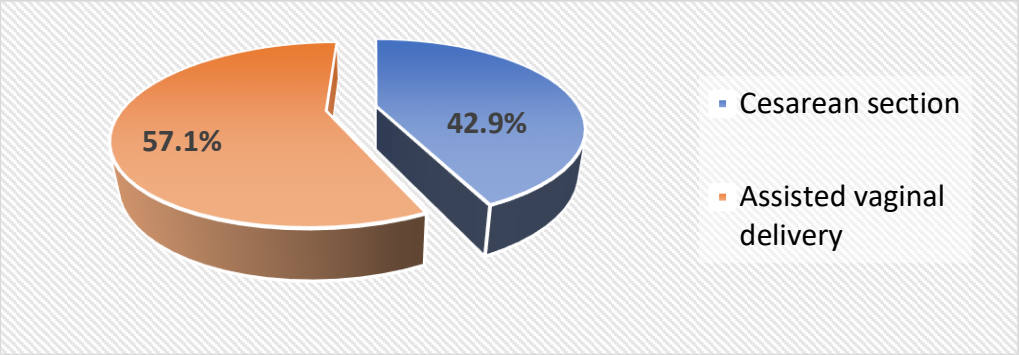
Among the indirect maternal death causes, cancer was the most common (n=3), whereas tuberculosis, bacterial meningitis and postpartum suicide resulted in one death each (Table 3, Paper 2).

The 13 (36.1%) coincidental death (causes unrelated to pregnancy) were transport accidents (n=2) and other accidents (n=4), cancer, representing brain and retroperitoneal tumors (n=6), and liver cirrhosis (n=1).

Mode of delivery

Of the 14 deceased women whose pregnancies resulted in a live birth or stillbirth, 57.1% (n=8) delivered by Cesarean section (CS) and 42.9% (n=6) had assisted vaginal deliveries (*Figure 20).*

***Figure 20**: Mode of delivery of maternal death cases, Georgia RAMOS14*



Four CSs were performed due to previous CS, one for pre-existing medical condition, one for preeclampsia, one due to obstructed labor and one without any medical indication. Of all CSs, 37.5% (n=3) were followed by post-operative infections, 25% (n=2) by postpartum embolism, one (12.5%) was related to complication of anesthesia and remaining 25% (n=2) were not directly related to complications of CS (indirect cause from breast cancer and TB).

Maternal deaths underreporting

Fourteen (60.9%) of the 23 maternal deaths documented in this study were officially recognized by the Georgian vital registration system as maternal. Only one of the eight late maternal deaths was reported in official statistics. Additionally, there were two early maternal

deaths of women while pregnant which went unrecognized by the official statistics (Table 4, Paper 2).

Incidence and Reporting

We found an overall MMR (early and late maternal deaths) for 2012 of 40.3 per 100 000 live births, which is a 38.5% reduction compared to the MMR of 65.6 per 100 000 live births in 2006 (*Figure 21*). Early maternal mortality declined by 40.8% (*Figure 22).*

Figure 21: *Overall maternal mortality ratios per 100 000 live births by RAMOS08 and RAMOS14 and official reports of maternal deaths in 2012 and 2006, Georgia*

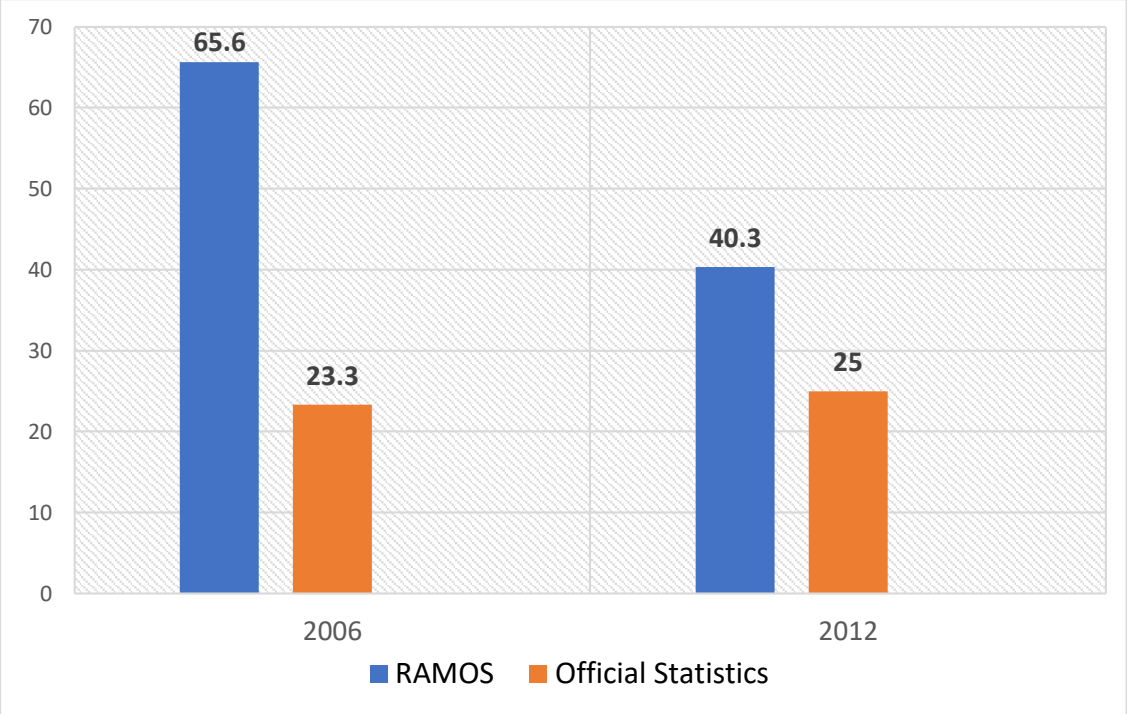
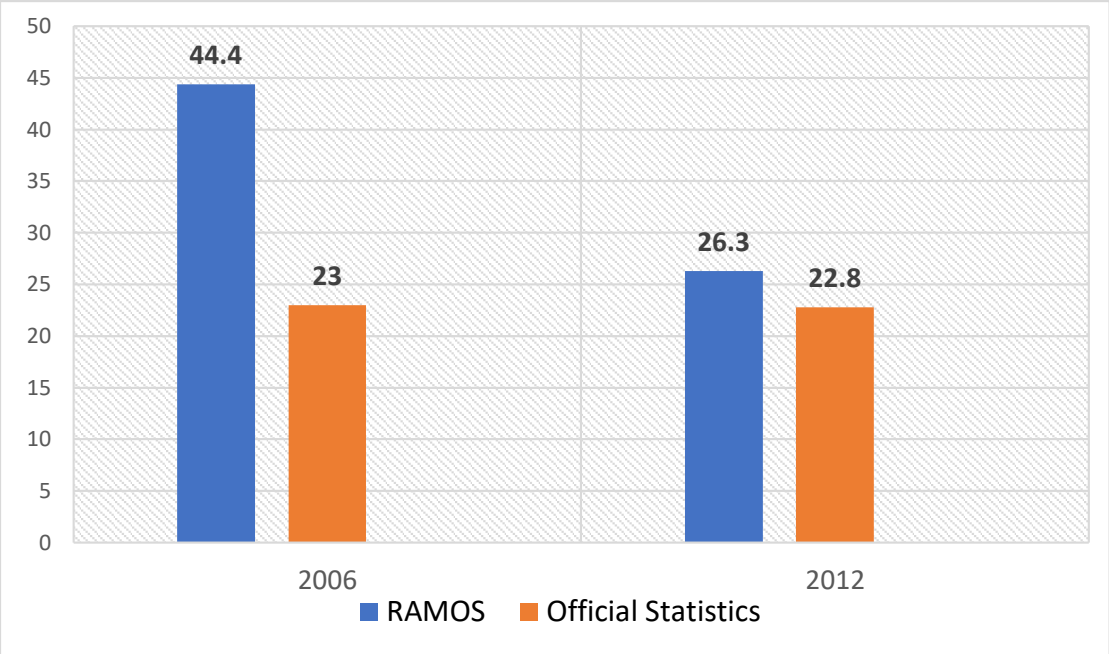


***Figure 22**: Early maternal mortality ratios per 100 000 live births by RAMOS08 and RAMOS14 and official reports of maternal deaths in 2012 and 2006, Georgia*

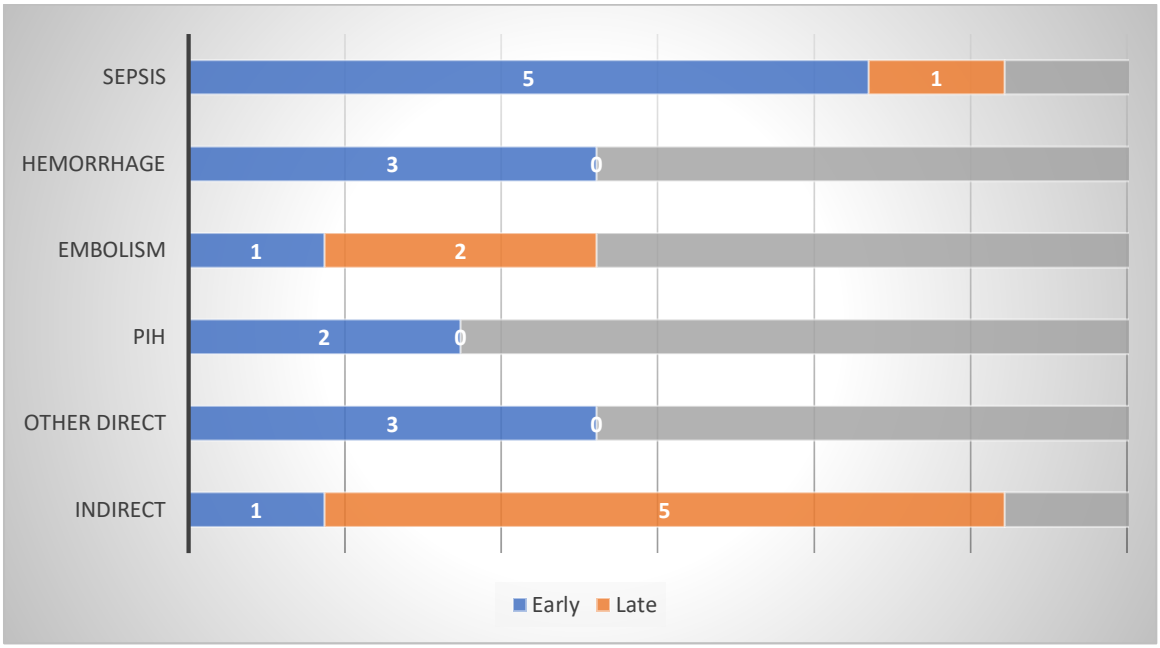


5.3 Study III: Audit of early and late maternal deaths in Georgia - potential for improving substandard obstetric care

Causes of maternal death

The leading causes of maternal deaths were sepsis (n=5), hemorrhage (n=3), pregnancy-induced hypertension (PIH) (n=2) and embolism (n=1). In other direct causes category, sudden death, unanticipated complication of anesthesia during delivery and complication following intrauterine fetal death, were one death in each (*Figure 23*). Direct causes of the late maternal deaths were: embolism (n=2) and sepsis (n=1). Indirect causes were cancer (n=3), tuberculosis (n=1), and postpartum suicide (n=1). Coincidental causes (13), unrelated to pregnancy, were due to transport and other accidents (n=6), cancer (n=6) and liver cirrhosis.

Figure 23: *Causes of Maternal Deaths by early or late time of death, Georgia RAMOS14*



Overview of care

The review of care for individual maternal death, that occurred in 2012 showed that suboptimal care was provided in 13 (87%) out of 15 early maternal deaths. Similarly, improvements in care which would have made a difference to the outcome was documented in two (67%) of the three late maternal deaths due to direct obstetric causes.

Table 2, of Paper 3 provides detailed review of care for each individual maternal death case.

Early recognition and appropriate management

We found that delayed recognition of a severe or life-threatening condition was a significant problem. Only one (4%) of 23 cases of maternal death was identified timely, 16 (70%) were detected with delays and for six (26%) indirect deaths, timely identification of the problem was not a relevant factor (Figure 3, Paper 3). Along with delayed recognition, deficiencies were evident in the management of complications in 65% of cases (Figure 3, Paper 3).

There were delays in recognizing all sepsis cases. A significant problem identified was timely recognition of the clinical signs suggestive of infection. Some of the cases evidenced a delay in both timely recognition and treatment of sepsis. Medical records were deficient in half of the sepsis cases, which were missing a full set of vital parameters on day preceding to or at a time when the diagnoses of infection were made. Additionally, gaps were documented in timing and spectrum of laboratory testing. No blood or other samples were drawn for bacterial culture for presumed infection in almost all cases. Although antibiotic therapy was initiated in most cases on the same day as infection was suspected, the delays and use of a proper antibiotic regimen was a significant problem.

Poor management was identified in all three fatal cases of obstetric hemorrhage. The management did not follow any of three basic principles of patient safety: the right patient, the right place, and the right procedure.

Poor prophylaxis and management were evident in two of three cases of thromboembolic maternal deaths but had probably no association with the last case due to the time lag of 133 days.

Finally, in-depth clinical audit disclosed substantial deficiencies in preeclampsia management. Two women who died from severe preeclampsia had inadequate monitoring of blood pressure and lack effective antihypertensive treatment.

Maternal referral

Along with deficiencies in early recognition and management of maternal complications, the study documented inappropriate and/or delayed referral in 11 (79%) out of 14 cases requiring referral. In six cases of early maternal deaths, the women were not referred in a timely manner or were referred to inappropriate level facilities.

6. DISCUSSION

The RAMOS14 is the second of its kind conducted in Georgia that provides accurate data and important insight into the numbers, patterns and causes of deaths among women of reproductive age and nationwide epidemiology of maternal mortality in 2012. The study methodology is strong and fully replicates the WHO-developed and tested approaches for maternal death investigation. All three studies presented in the thesis are based on the second national RAMOS14.

6.1 Strengths

Our research is an important step towards better understanding of the reproductive age women's health risks based on reliable data on mortality, the cause of death and risk factors contributing to these deaths. All these are of critical importance to inform evidence-based health policy and develop robust strategies addressing avoidable premature female and maternal mortality. Our study contributes to scarcity of data to the cause-specific mortality patterns and trends over time in reproductive aged women in Georgia. Furthermore, our scientific work sheds the light on levels and trends of maternal mortality underreporting in vital records, the pattern of causes of maternal deaths, maternal deaths in the general mortality of women of reproductive age and importantly, identifies main gaps in quality of health care services and improvements required.

While the findings from our research contributes to global and regional evidence, the results presented here primarily serve as the baseline evidence for tracking progress toward the broader national and global sustainable development goals.

The major strength of our research includes the use of the national representative data from the second RAMOS14. Therefore, the study offers high potential for generalizability of our

findings to all settings with similar health system development. All deaths of reproductive-aged women in 2012, investigated and presented in our studies, was the outcome of the complex process grounded on triangulation of multiple data sources: the civil registration vital statistics (CRVS) mortality electronic dataset, routine health statistics and surveillance data from the National Center for Diseases Control and Public Health (NCDC&PH), hospital and ambulance service registers electronic datasets, regional death registers, community informants contacted during the field investigation. The triangulation of diverse sources minimized the likelihood of maternal death case missing and underreporting. The additional detailed information on mortality death cases was gathered, cross-checked and verified through verbal autopsy (VA) with family members of the deceased, medical records review, and interviews with medical professionals, which contributed to the accuracy of maternal death case identification.

The VA interviews were conducted by well-trained and experienced interviewers with medical background, yielding the high response rate of 96.2%. Adequate quality control measures were adopted throughout data collection and processing. The RAMOS14 used a unique verbal autopsy questionnaire for collecting data related to circumstances of death, regardless of its cause. The validated VA instrument, developed for the first National RAMOS08 in line with the Adult Module of the WHO international standard VA questionnaire. The additional questions on reproductive system cancers, injuries, as well as household living standards and on history of use of health care services prior to death incorporated in the instrument, was well suited to collect important quantitative and, in part, qualitative details on the pre-mortem illness symptoms and signs, sequence of events, health care experience, as well as individual and contextual factors, contributing to death.

The underlying causes of maternal deaths were assigned by two certified expert clinicians applying the standard rules of the International Classification of Diseases, 10th revision (ICD-10). The discrepancies in coding were resolved by a third physician who adjudicated the final diagnosis. The described multistage process of cause of death ascertainment was critically important for addressing the common limitation of other studies and minimizing the chances of misclassification.

Our study indicates that VA is a valid data collection mechanism and a feasible tool for filling in existing gaps in national and regional cause-of-death data, when medical certification of the cause of death is unavailable or compromised by the substantial use of ill-defined codes.

This is one of the very few studies linking the data derived from official and VA sources to assess the reliability and validity of the mortality data generated by the CRVS system in Georgia. Our findings highlight that, in the absence of "gold standard" sources such as post-mortem pathological autopsies, data linkage between these two sources is a viable and promising technique to provide critical insights into the strengths and limitations of the registered cause-specific mortality statistics.

Replication of the first National RAMOS08 methodology by the repeat RAMOS14 was highly conducive to compare the 2006 and 2012 cause-of-death data derived from VA as well as comparison of trends in maternal mortality underreporting and causes of maternal death. Additionally, the RAMOS14 allowed access to individual patient records. This provided an opportunity to describe the characteristics and circumstances surrounding maternal death. Importantly, this study provides a platform for identifying a range of issues in the health care service delivery that can be addressed in the future efforts to reduce maternal morbidity and

mortality. The fact that detail hospital and antenatal care data were analyzed makes it possible to propose changes in hospital and primary health care policies and practices that may further reduce avoidable maternal deaths.

6.2 Limitations

Our research has several limitations. First, in the original sample, underlying causes of death could not be determined for 35 out of 913 potentially eligible women because of a failure to reach their families and complete VAs. However, it is unlikely to expect that such a small percentage of missing causes (only 3.8%) will significantly bias our findings. In addition, 39 deaths (4.4%), lacking clear symptom patterns, were assigned to ill-defined codes in VA data. Second, the study did not include a detail review of medical records or characteristics of care for late maternal deaths due to indirect causes, therefore, it is not known to what extent the missing data may have biased the results. Additionally, postmortem autopsies - important to examine the cause and factors that contribute to death - were not performed in any of the 23 maternal deaths cases, due mainly to cultural challenges related to postmortem autopsy practices in Georgian society. Finally, no population-based maternal mortality study was conducted after RAMOS14, as such it is difficult to understand if the developments are going in the right direction and therefore, repeat RAMOS studies may be required.

6.3 Leading causes of death among women of reproductive age and burden of maternal disorders in the overall mortality structure of reproductive age women

Non-communicable diseases are the leading causes of death in reproductive age women

Non-communicable diseases (NCDs) represent the new and increasing challenges that are emerging in women's health. With two-thirds of all deaths among women of reproductive age, NCDs are the leading cause of death identified by our study. This finding is in line with the global diseases burden [105] and the rapid rise in premature deaths from NCDs in reproductive-aged women [106-108].

While NCDs affect persons of all countries, low- and middle-income countries, such as Georgia, are more strongly affected than high-income countries by the burden of NCDs, due to fewer resources in prevention, promotion and provision of care. Our findings reflect the deficiencies in health system, inadequate early diagnoses and prevention of NCDs as one of the most neglected areas of public health and Primary Health Care (PHC) in Georgia. With the introduction of the Universal Healthcare Program (UHC) in 2013 and expansion of benefit package for its citizens, including coverage for essential medicines for chronic diseases in 2017, the government has made an important step towards protecting the population from the financial risks of health care costs and reducing inequalities in health care coverage. Despite this progress, incentives in the system for patients and providers still strongly favor emergency and inpatient care, leaving health promotion, diseases prevention and early diagnoses underfunded [109 -110].

The sex-specific analyses of NCDs in Georgia shows similar patterns as observed in other countries of the Former Soviet Union (FSU). Specifically, while higher percentages of men than women in most age groups engage in behavioral risk factors for NCDs (like tobacco-

smoking, alcohol consumption, insufficient levels of physical activity, insufficient intake of fruit and vegetables, adding salt and frequent consumption of processed foods) women appear to be more exposed to biological risk, especially in obesity and raised cholesterol [111]. Importantly, prevalence of tobacco use for men in the 30–44 age group decreased from 2010 to 2016, while tobacco use for women appears to have increased in all age groups. This is alarming as studies show at least a twofold risk for cervical pre-cancerous lesions and cancer among current smokers compared to non-smokers [112-113]. Findings from the same analyses of STEP data highlight women's higher frequency of interaction with health-care services and initiation of measurement for biological risk factors earlier than men. This indicates a substantial scope for future improvements in uptake of cost-effective interventions like NCDs Best Buys and other interventions recommended by WHO [114-116] through improved primary health care (PHC) and health system response strategies tailored to country specific context.

Cancer-related causes of death in our study is concerning. Contributing to almost half of all deaths, with breast cancer being the leading, followed by cervical cancer, is indicative of slow progress in implementing quality-assured organized cancer screening program, early diagnoses and quality of cancer treatment as well as low awareness of cancer symptoms and delays in seeking care. The findings from our study are in line with global and European estimates which rank breast and cervical cancers among the leading causes of death in reproductive-aged women [117, 107]. However, there is a big gap in incidence and mortality levels between Georgia and Western European countries due to differences, for example, in HPV vaccination rates and screening quality and coverage. The HPV pilot demonstration program which started in 2017 with support from the Global Alliance for Vaccines and Immunizations (GAVI) is an opportunity to build a strong case to support nation-wide introduction of HPV vaccine and justify allocation of necessary funds. Despite well-established effectiveness, impact, and safety

of the quadrivalent HPV-vaccine decisions [118] to introduce this vaccine may be influenced by public distrust, fake news and criticism of HPV vaccination. Building public trust in Georgia will require implementation of tailored communication and community engagement strategies based on formative research to understand concerns of parents and other population segments. Strengthening national capacities to effectively respond to vaccine safety events is of paramount importance, as well**.** As shown by experience from some European countries even after successful launch of the HPV-vaccination program and high uptake of the vaccine, sustaining or rebuilding public trust in vaccines is an ongoing effort [119]. Some radical improvements are also needed in national policies and resources allocations for organized, population-based, quality-assured cervical cancer screening program. Similarly, for breast cancer, persistent low mammography screening coverage, limited geographical availability and late diagnoses warrants critical evaluation of effectiveness of current breast cancer control strategy. Multidisciplinary teams/boards are crucial for diagnoses, treatment decisions and outcomes and proven to conform to evidenced-based guidelines then individual health care provider [120]. In Georgia, fragmented breast cancer services in multiple private health care institutions with limited volume of patients, absence of multidisciplinary teams raise concern on provision of high-quality, consistent, coordinated and cost-effective care to the patient across the breast cancer care pathway. In general, adherence to evidence-based practices need to be promoted, discouraging policies and practices with no evidence on effectiveness (e.g. screening for prostate cancer) so that the country uses limited resources effectively and efficiently for high-impact interventions (for example, investing in mmonitoring & evaluation and quality assurance systems for breast and cervical cancer screening programmes, robust cancer surveillance data to inform national polices).

The 73th World Health Assembly passing a resolution calling for elimination of cervical cancer and adopting a strategy to make it happen is an opportunity for Georgia to restate its commitments to elimination and take national action towards the 2030 global strategy targets of 90% of girls fully vaccinated against HPV by the age of 15 years, 70% of women screened for cervical cancer at 35 and 45 years of age, and 90% of patients receive treatment for cervical cancer in every country [121].

Maternal mortality declines but remains high

While maternal disorders remained in the top ten causes of deaths among women of reproductive age, in our study, rank decrease was observed for maternal disorders, from place five to place nine between 2006 and 2012. This observed decline in maternal death mirrors the global trends in maternal mortality with overall decrease from 1990 to 2015 in global maternal deaths roughly by 29% [122]. Maternal disorders represent 7% of all causes of deaths globally and 0.69% of total deaths in Central and Eastern Europe and Central Asia.

With the reduction of early maternal mortality by 40.8%, from 44.4 per 100 000 live births in 2006 (RAMOS08) to 26.3 per 100 000 in 2012 (RAMOS14), the MMR in our study reflects the same level of maternal mortality reported from middle-income countries in Central and Eastern Europe, Caucasus and Central Asia [123-124]. However, the observed ratio is twice higher than most high-income countries [125-126] and far from the ratio being targeted for 2030 in Georgia [127]. Although the largest number of births still occurs among women between the age of 20 - 29 years, we found the highest age-specific maternal mortality ratio in the older age groups (35–39 and 40–44) and the lowest in age group 25-29.

Like other studies that examined the effect of income inequality and maternal health outcomes [128-129], maternal deaths were higher in women with low income levels, with

one third of maternal deaths occurring among women living at subsistence or below subsistence level. Even though Georgia has coverage for maternal health care, our findings shows that there is an urgent need to address this vast inequity and decrease the risk of maternal death based on individuals' low socioeconomic factors.

The challenges associated with still high maternal mortality rates in Georgia and actions taken to change the current MMR are discussed in detail in the following sections.

6.4 Completeness of pregnancy-related deaths registration

Significant improvements were observed in death registration coverage and reporting of pregnancy-related deaths. Underreporting and misclassification of late maternal deaths alongside with indirect obstetric causes and maternal death outside of heath care facilities remains a challenge.

All 36 pregnancy-related deaths included in our study were officially reported in the vital registration system, whereas only 85.7% were reported in 2006 [81]. This represents a significant improvement in death registration coverage in Georgia, reported as well by WHO (98%) and reflecting results of the CRVS reforms introduced since 2010 [130]. Although all the 36 deaths were registered in the vital statistics, only 14 deaths were recognized as maternal with 13 early and one late maternal deaths. Thus, the study revealed 9 (2 early and 7 late) additional maternal deaths based on VA and comprehensive case review documenting 39.1% overall underreporting of maternal deaths by the official statistics. Under-reporting of maternal causes of deaths in the routine registration system is observed in high-income countries, varying from 30% to 50% and largely attributed to artifacts in cause-of-death certification and coding practices [131, 125].

Underestimation of maternal deaths varied by age, place, timing and cause of death, with the largest differences seen in 34-39 age groups (75.0%), non-facility-based deaths (71.4%), late deaths (87.5%) and those from indirect causes (83.3%). Of the 8 (34.8%) late maternal deaths identified in the present study, 87.5% (7) went officially unrecognized and were misclassified in other ICD–10 chapters that is comparable to 90.0% of late maternal deaths officially unreported in 2006. For the early maternal deaths, the study revealed underreporting by only 13% in contrast to the 48% observed in 2006.

These findings are in line with other studies demonstrating late and indirect maternal deaths being commonly unreported deaths [132-133]. In relation to indirect maternal deaths, there is also observed inconsistency in reporting causes of maternal deaths by the vital registration systems. For example, some countries include psychiatric disease and hormone dependent malignancies [134-135] as an indirect maternal death, resulting in higher reported maternal mortality rates. In our study both were included as indirect obstetric causes. When making international comparisons it is important to adjust for these inconsistencies.

The current study showed the substantial improvement in maternal mortality reporting (39.1% underreporting) since 2006, when the vital registration system failed to report 64.5% of maternal deaths. The decrease in unrecognized and misclassified maternal deaths could be largely attributable to the remarkable progress achieved by CRVS system in death registration completeness, and introduction of important elements of active maternal mortality surveillance to strengthen maternal death identification, notification and review. Since RAMOS08, the National Statistics Office has started matching of the death records of women of reproductive age against the birth and fetal death records by woman's ID number to identify deaths to delivered women within one year postpartum as well as triangulation of data with NCDC&PH.

Implementing data linkage and especially confidential enquiries in all European countries would substantially improve the ascertainment of maternal death [136,126].

Notwithstanding significant improvements, addressing misclassification of deaths due to maternal causes requires further work. Despite a recent improvement in the death certification process related to the introduction of the electronic notification system which requires the completion of the pregnancy check-box and its known effectiveness in maternal deaths identification [137], most death certificates of women while pregnant or within 1 year postpartum lacked the pregnancy status specified, leaving the pregnancy check-box empty. In addition, in most cases autopsy reports were unavailable due to its absence in routine practice. Any inference about the temporal association between the death and pregnancy in the official reports are based solely on data matching and/or the ICD-coding of the underlying cause of death. However, some maternal deaths cannot be identified through record linkage as they do not generate a record of pregnancy outcome. This is particularly challenging in case of the deaths during pregnancy, after abortion or ectopic pregnancy, gestational trophoblastic disease and any deaths due to indirect obstetric causes. Linkages with other registries, such as abortion or using verbal autopsies to identify abortion related cases is of importance as a high proportion of deaths relating to abortions tend to be not registered as maternal deaths [138-139]. Using death certificates alone, only 12% of deaths following miscarriage or ectopic pregnancy and 1% of deaths following pregnancy termination could be identified without record linkage [140].

The study identified the gaps in the system to collect cause-of-death data on out-of-hospital pregnancy-related deaths in Georgia. Of the 36 pregnancy-related deaths identified in the study, from 11 occurring at home 6 cases (3 due to embolism with 1 early and 2 late deaths, one early sudden death and 2 late indirect deaths) were classified as maternal by our study, of which only

2 were officially reported as maternal deaths (1 early from postpartum embolism and 1 late from leukemia after ectopic pregnancy). Of the remaining 5 home deaths classified as co-incidental in the study, 3 deaths (2 from external causes and one from cancer) were correctly classified by official sources based on the data matching, whereas 2 deaths during pregnancy (from external causes) went unidentified.

Studies demonstrate that countries routinely monitoring maternal deaths using audits or routine linkages, or confidential enquiries, or periodic VAs have identified more maternal deaths compared with the civil registration system and have higher reported MMR than countries that have not implemented these initiatives [141]. Active and accurate surveillance of maternal deaths is necessary as it leads to important improvements in policies and practices for maternal health care.

We found inadequacies in quality of mortality data, with completeness of ascertainment and quality of coding being one of the main issues of maternal mortality measure. Based on cause agreement and misclassification analyses, maternal disorders were originally miscoded to various specific or unspecified categories, but mostly to ill-defined and unspecified external causes. Majority of leading causes of death such as breast, cervical, uterine, and brain cancers, cerebrovascular diseases were also miscoded in the CRVS with excessive use of ill-defined codes. The findings from our research are consistent with earlier studies documenting overuse of ill-defined and "other" unspecified codes undercounting of maternal causes in the CRVS and largely attributed to gaps in cause-of-death certification and coding practices [142-144, 77].

The results of our study indicate importance of periodic assessments of the quality of routine mortality statistics for reporting maternal deaths, undertaking regular underreporting studies

and related public health actions. The study also underlines the need for pre-service and continuous training of physicians and coders in the cause-of-death certification and coding practices [143, 145].

6.5 Causes of maternal deaths

Direct obstetric causes were principal causes of death with sepsis and hemorrhage being the leading, but indirect causes are on the rise

Our study identified direct obstetric causes accountable for almost all early maternal deaths, while two thirds of late maternal deaths were due to indirect causes. Despite increase in indirect causes, this trend is similar to the RAMOS08 findings as well as in line with other studies that demonstrate that majority of maternal deaths are still due to direct obstetric causes [7,125]. Among direct causes, infection and hemorrhage ranked at the top, followed by pulmonary embolism and pregnancy induced hypertension. Although the causes of maternal deaths vary substantially between countries, in a WHO systematic review of global causes of maternal death, about 73% of all maternal deaths were due to direct obstetric causes [7] with obstetric hemorrhage still being the most frequent cause of death, with the rates highest in Africa (33.9%) and Asia (30.8%) and 16.3% in developed regions. Analyses of global causes of maternal death showed that a quarter of all hemorrhage deaths happened during pregnancy, and the remainder in the intrapartum or postpartum period. In our study, hemorrhage was largely associated with induced and spontaneous abortions or miscarriage, with only one case of postpartum hemorrhage. By contrast, in 2006, hemorrhage mainly occurred during or after labor and delivery. Elevated risk of death after pregnancy loss mostly relate to deaths from external causes: suicide, homicide, and accidents compared to both delivering women and women who have not recently been pregnant, pointing to psychological effects associated with pregnancy loss that may contribute to deaths resulting from self-destructive or risk-taking

behavior. The maternal deaths related to obstetric complications of induced and spontaneous abortion observed in high incidences in developing countries, although very rare in developed regions, still may occur [146-148]. Combined, induced and spontaneous abortions of maternal deaths in our study was higher (17.4 %) than the worldwide average (7.9%) and developed regions average (7.5%) for the period of 2003-2009 [7]. However, proportion of maternal deaths due to induced abortion (4.3%) was lower than worldwide average (13%) and similar to developed region and Eastern Europe average of 4% and 3%, respectively. In the past decades, globally, policy and programmatic focus has been mainly on postpartum hemorrhage. Georgia also made a focus to improve quality of obstetric care targeting training of obstetric service providers on managing postpartum hemorrhage and pregnancy induced hypertension, rolling-out implementation of clinical practice guidelines to standardize management of these emergency obstetric conditions. We believe that these capacity building efforts contributed to decline in postpartum hemorrhage-related maternal deaths in the country. Our findings substantiate the need and importance of improving surveillance and immediate treatment of especially second trimester spontaneous abortion to prevent related unexpected maternal deaths and achieve better pregnancy outcomes in Georgia. While country experienced a welcome decrease in abortion rates over the past decade and increasing contraceptive use and the availability of more effective forms of contraception had reduced the number of unplanned and unwanted pregnancies. Further improvements in this direction are needed. Still, over a third of all married women have unmet need for contraception with the significant need among women with rural residence, low education and poor wealth quintiles [149].

Our data also point to the fact that sepsis represents a major threat to maternal health in Georgia. Although sepsis remains the third most common direct cause of maternal death globally, until recently it received less attention, research and programming both in Georgia and worldwide. The risk of death from maternal sepsis is low in developed countries.

Respiratory infections are the dominant sepsis cases with maternal mortality and severe maternal morbidity being more significant than due to genital tract sepsis [150-151]. This contrasts with our study where post-operative infection was the source of sepsis. It must be noted that pandemic and seasonal influenza result in significant morbidity and mortality. In 2009, maternal mortality ratio sharply increased in Georgia explained by several reasons, including improvement of registration of deaths, but primarily due to pandemic influenza (H1N1). Similarly, increased hospitalizations and deaths among pregnant women were reported by many countries when the 2009 H1N1 pandemic strain was predominantly circulating virus, with an increase in maternal mortality ratio [152-153]. Evidence is accumulating on increased risk of maternal deaths and of being admitted to the intensive care unit in pregnant women with Covid-19 versus without it. Worsening global maternal outcomes, especially in low- and middle- income countries are expected due to Covid-19 pandemic as increases in maternal deaths, stillbirth, ruptured ectopic pregnancies, and maternal depression are demonstrated by studies from several countries [154-157]. Reduced access to care, driven by concern about the risk of acquiring COVID-19 in health-care settings, restrictive measures introduced by the governments to limit the spread of the infection, such as reduced public transport and advice to stay at home [158-160] were contributing factors. What role COVID-19 infection has in the overall causes of maternal death is yet unknown and will require rigorous population-wide surveillance data from many countries.

Known risk factors for maternal sepsis are younger age and caesarean section [151, 161], also supported by our study. Importantly, maternal mortality was 14.0 per 100,000 live births for CS and 12.3 per 100,000 for vaginal births with significant proportion of women dying from maternal sepsis followed by caesarean section delivery. Despite the risks related to cesarean sections for maternal and newborn morbidity and for subsequent pregnancies [162-164], a

steady and unprecedented rise in the rate of CSs has been observed globally over the past few decades. The increased CS rate from 20.7% (2006) to 36.7% (2012) and reaching an average of 44% by 2016 [165] is worrying. WHO statement on CS rates clearly states that CS should be undertaken when medically necessary, and rather than striving to achieve a specific rate, efforts should focus on providing caesarean section to all women in need [166]. While in 2006, RAMOS08 found that the majority (95%) of CSs were emergency and life-saving, our study revealed that only a quarter of CSs were emergency interventions performed on the same day the women initially presented for care. Clearly, comprehensive efforts to reduce CS rates focusing on limiting unnecessary cesarean deliveries - targeting the drivers such as maternal request, medicolegal reasons, provider and patient-driven medicalization of birth - are needed. Introduction of the Robson Classification – an internationally applicable CS classification [167] - will be needed to audit CS and improve analysis of local practices.

In the last two decades, an increase in indirect maternal deaths has occurred globally, making up almost one-third of all maternal deaths [7]. Indirect maternal causes were responsible for 26.1% of maternal deaths in Georgia, in line with this global trend. The obstetric transition—a shift from maternal deaths due to direct causes, like hemorrhage and infection, to patterns of maternal deaths due to indirect causes, like NCDs is observed [84]. Non-communicable diseases represent a significant global public health challenge and are responsible for nearly 90% of deaths and 84% of years lived with disability in the WHO European Region. The share of NCDs in the overall disease burden is increasing from year to year. In the indirect maternal death category, cardiovascular conditions, anemia, neoplasms and diabetes featured amongst the commonest reported causes of death globally. Alarming result of our study is cancer-related causes of death among women of reproductive age. Cancer contributes to almost half of all eligible deaths, with breast cancer being the single most important cause of death. In Georgia, the largest group of indirect maternal deaths was attributed to cancer, also

found in several population-based studies reporting on specific causes of pregnancy-related deaths due to NCDs [168-171]. Global trends like urbanization and women having children later in life, behavioral risk factors including tobacco and alcohol consumption, as well as increasing obesity can accelerate the occurrence and consequences of cancer and other NCDs in pregnancy and postpartum. Similarly, in Georgia, wider adoption of lifestyle choices such as unhealthy diet, low physical activity, smoking, and alcohol use, with associated raise of metabolic risk factors - lipid, glucose and blood pressure profiles, have coincided with a marked shift in the burden of disease towards NCDs, currently comprising 93% of total deaths, with 19% of female premature deaths [172-173]. Indirect causes, primary contributor to late maternal deaths documented in our study, with the leading cause being malignant neoplasms, is in line with a prior study from Italy, where cancer was a leading cause of late maternal deaths [174]. Our finding reflects deficiencies in health system, particularly primary health care with inadequate capacity of early detection and prevention of NCDs, the divide between primary health care and public health and hospital services, and lack of continuum of care – from clinical prevention through early detection, screening and treatment. On the other hand, maternal health services traditionally have focused on immediate needs of pregnant women and their fetuses. Moving forward, a comprehensive life course approach [175] is required with effective NCD interventions during pregnancy and postpartum for immediate effects on pregnancy outcomes and integrated continuum of care for health promotion, prevention and effective clinical interventions at all stages of life.

6.6 Quality of obstetric care

Gaps in quality of care and preventability of maternal deaths point out to urgent improvements in quality across the continuum of maternal health care

Most countries in the WHO European Region are at the stage whereby maternal mortality has been reduced from a moderate to low level, and to facilitate further reductions in mortality, improvements in the quality of healthcare and elimination of delays in a health system are key factors to address. Our study showed deficiencies and delays at all stages of provision of care. Of all 23 maternal deaths, any type of delay related to health care seeking, service accessibility or quality of medical care was identified in overall 73.9% cases. The main user-side factor affecting the early decision to seek care, thus the first delay, was women's or their caregivers' failure to timely recognize warning signs or the severity of pregnancy complications. This factor contributing to delayed care-seeking among half of all mothers, particularly among rural community, economically disadvantaged and ethnic minority groups, points out on the inadequate level of education provided during antenatal care.

While analyzing a third delay (i.e. delivery of adequate care within the health facility) – the focus of our study - we assessed the care at the first admission to a facility and at the referral hospital, including timely recognition, appropriate management and treatment delay, and any delays in transfer to another higher-level facility. Lack of effective and timely care at any of these time points may aggravate a patient's condition and result in a poor outcome. For example, substandard care wherein improvements could have made a difference to the outcome was found across all sepsis cases. Delay in recognition and diagnosis of sepsis was responsible for majority of maternal deaths from sepsis documented by our study. Similarly, early recognition and adequate assessment of blood loss in the management of obstetric hemorrhage

as well as inadequate clinical management were major factors leading to the death of women from obstetric hemorrhage.

WHO standards for maternal and newborn care highlight evidence-based practices for routine care and management of complications, actionable information systems and functioning referral systems along with competent and motivated human resources, and essential physical resources while experience of care including effective communication, respect and preservation of dignity and emotional support as critical factors for quality service provision [176]. Furthermore, systematic review of a "third delay" cites human resources as one of the most common barriers, with inadequate training resulting in fatalities or near-miss events [177]. In this category, studies highlight limited educational opportunities for health workers due to the absence of continuous medical education programs, formal training with inadequate proficiency in acquisition of clinical skills by medical graduates, innovative medical curricula and methods of learning, and poor access to up-to-date educational resources [178-182]. In Georgia, while the legislation clearly states that continuous medical education is integral part of medical activity and an essential component of professional qualification of physician, it is not legally mandatory and physicians' participation in educational activities is voluntary. The motivation to participate in the continuous medical education programs is further influenced by the fact that once certification for medical practice is granted, it is valid indefinitely [183] in addition to financial challenges (e.g. low salaries, no budget lines for CME/CPD in health care organizations). Regulatory changes, including re-certification and re-licensing and accumulation of continuing medical education credits as a mandatory condition of re-certification and re-licensing, standards on the use of continuous medical education, as well as relevant incentives for health care providers in line with the best practices in most of the European Union and EEA countries [184], should be introduced and operationalized in

Georgia. These policy changes among others are of critical importance to build a resilient health care workforce and to achieve high quality universal health care set by the country.

A culture of continuous measurement and quality improvement is a prerequisite for improving health outcomes and reducing preventable maternal mortality and morbidity. The efforts of quality improvement in Georgia largely focused on technical factors such as structural (e.g. facility infrastructure, equipment) with less attention to processes and systems inside of health facilities, including lack of good quality, meaningful and timely data collection on clinical processes necessary to ensure baseline and ongoing monitoring for areas where safety and quality improvement should occur. Policies enacted by MoLHSA in 2012 and 2017 set the requirements to establish quality committees, staff required and develop plans of actions. Policy to report maternal and newborn care Clinical Quality Indicators and making it as a requirement for selective contracting of health care facilities by the Ministry are steps in the right direction [185]. Since 2015, several initiatives have been implemented to reduce avoidable maternal deaths. These initiatives include in-service training courses for obstetrician-gynecologists, midwives and intensive care specialists and the updating of national clinical practice guidelines.

Effective methods to understand barriers and drive quality improvement efforts such as facility-based maternal near-miss case review cycle [88] as well as few national-level initiatives aiming to improve quality of care in Georgia have been implemented building a foundation to grow. However, as documented by the studies, the successful implementation of quality improvement approaches will require along with building knowledge and skills [186-187] a drastic change in attitudes and culture, moving away from blame and punishment of single individuals to looking to the health system failures and finding solutions at the organizational level [188-190]. Furthermore, instilling culture of quality improvement, its concepts and methods and

contexts in which these approaches should be used to maintain and improve quality and safety, need to start from undergraduate medical education [191-194]. While acknowledging that there is still the lack of standardized and universal undergraduate quality improvement teaching in medical schools [195] adapting content of medical curricula to include quality improvement concepts and methods in clinical courses and requirement to implement quality improvement initiatives in the clinical area in the postgraduate medical education will be important steps in reforming medical education in Georgia.

Our study findings demonstrated that facility of the first admission or referral facility were not capable of providing the required level of care. For example, facilities that managed the second trimester miscarriages and related complications, such as bleeding and uterus perforation leading to maternal death, were basic maternity units with limited capacity and unequipped with resources to manage the women at risk, to handle complications or to stabilize the patient before referring to another facility. Studies carried out in the USA and Japan demonstrate the effect of hospital volume and regionalized approach on maternal morbidity and mortality and strong association between maternal medical or obstetric conditions known to benefit from multidisciplinary expertise and appropriate level of maternal care [196-199]. A principle of regionalization is a risk-appropriate care for women at risk for maternal morbidity at hospitals classified based on available clinical staff and resources as basic care, specialty care, subspecialty care and regional perinatal health care centers. At the same time collaborative model of care between different levels, including plans of care for transfer of women with complications to specialty and subspecialty care, and collaborative quality improvement initiatives, is a marker for success in maternity care.

Georgia has made a fundamental change to an organization of maternal and newborn care service delivery model and introduced regionalization in 2017. This includes stratified system

for levels of maternal and newborn care with high-risk patients triaged to hospitals with appropriate resources and expertise, designations for levels of maternal care using standardized definitions for staffing, center capabilities, clear guidance where patients with specific risk factors should deliver, and equitable geographic distribution of full-service maternal care facilities. These efforts led to improvements in facility infrastructures, clear scope of practice and definition of competencies at each level along with a greatly strengthened referral system and creation a coordinated system of care between different facility levels. However, desired gains in maternal health outcomes across Georgia will require constant improvements in quality and safety at multiple levels of the health system.

Another important finding of our study is deficiencies in primary health care. Although the risk factors were present in both cases of preeclampsia in our study, no increased schedule of antenatal care for these women with pre-existing hypertension was provided, and no visits were scheduled between 28 and 33 weeks of gestation. It should be noted, however, that the clear majority (87.0%) reported to receive antenatal care with most women (73.9%) initiating antenatal care early, within the first 12 weeks. By comparison, in 2006, among women who died of maternal causes after delivery, only 41.9% had received early antenatal care, while 25.8% had no care as documented by RAMOS08. Studies have shown that non- or under-attendance at antenatal care carries a substantially elevated risk of severe adverse pregnancy outcome [200-201]. Along with inadequate quality care, including poor provider-patient communication, financial constraints due to out-of-pocket (OOP) payments for ANC is an important barrier for antenatal care attendance, particularly among the poor and marginalized [202-204]. Despite a notable decrease in OOP health expenditure, health system financing in Georgia is still dominated by OOP payments [33] and it is one of the highest in the European Region [205]. At the time of study, the national program for pregnant women covered only four antenatal care visits, leaving high-risk women to pay out of pocket for any visit beyond

the four covered by the government. However, enormous efforts were made by the government to improve financial protection of pregnant women and systematic monitoring of pregnant women and fetuses. The new policy released by the government in 2017 recommends 8 antenatal contacts with the health-care provider, of which six taking place in the 3rd trimester, in line with the WHO guideline [58], and with state funds fully covering these visits [57]. Nevertheless, about one fifth of pregnant women do not complete at least four antenatal visits and about 15% do not initiate care in the first trimester [166]. What impact the new ANC policy will have on maternal health outcomes needs to be assessed. Our findings indicate that to accelerate progress in the prevention of avoidable maternal mortality, Georgia should achieve its target of 100% of at least four ANC visits by 2030 [60] and importantly, improve quality of ANC focusing on timely detection of high-risk pregnancies and co-morbidities and content of ANC.

The high cost of abortion procedure, which is not part of benefit package in the UHC program and financial barriers to safe abortion services was a contributing factor to the death of woman from abortion related complication. A woman from a socially vulnerable family (living below the poverty line) self-induced abortion to terminate unintended pregnancy. She delayed the abortion until 18 weeks of pregnancy in anticipation to procure resources for abortion services. The woman terminated an unintended pregnancy by self-administering 10 tablets of misoprostol. Delayed health care due to financial barriers is an underling factor in this fatal outcome. Another contributing factor is unregulated access of misoprostol and in general, prescription drugs in pharmacies, without doctor's prescription. As such, often, women with limited access to abortion services turned to self-administration of the drug for pregnancies termination.

A Prescription Order reform was initiated by the Georgian government in September 2014, which prohibits selling the "prescription only medicines" without a provider's prescription. The restrictions, however, do not necessarily reduced access. The prescription drugs may still be available illegally without prescriptions if monitoring mechanisms for implementation of the order are not in place or adequately performed. Georgia still faces challenges with implementation of the prescription reform.

The universal health care program (UHC), introduced in 2013 by the Georgian government, strives to provide universal coverage for the population through a tightly defined package of publicly funded benefits and has made considerable progress [33]. Although UHC extended the breadth of coverage to almost the whole population, including more comprehensive cover for lower income households, the costs of abortion, family planning services, and products even for socially disadvantaged people are not covered. An assessment of sexual and reproductive health services and policies related to UHC in selected countries of Eastern Europe and Central Asia - Albania, Azerbaijan, Kazakhstan, Kyrgyzstan, the Republic of Moldova and Romania - identified important gaps in sexual and reproductive health (SRH) services included in the health benefit packages with contraceptives not or not fully included in the health benefit packages in many countries, and absent coverage for abortion services [15, 206]. It is very clear that progress towards UHC cannot be achieved without advancing policies and program that improve women's lives and rights.

The low outpatient visits per capita compared with the European Union average points out to the weakness of PHC in Georgia. Although PHC covered under UHC, quality is an important factor determining the low utilization [207]. Critical aspects of care among the late maternal deaths in our study were indicative of deficiencies in preconception and postpartum care in Georgia, where an improvement might have prevented or limited some maternal deaths.

Preconception care is uncommon form of care in Georgia and although preconception visits are being promoted in some EU countries they are still underutilized in many European countries [208-209].

Only 24% of women received postpartum care after 4 weeks [210] while WHO recommends postpartum care between days 7–14 after birth, and six weeks after birth [211]. Fragmentation and poor continuity and lack of engagement of family doctors in postpartum care were the characteristics of maternal health care showed by our study. Electronic maternal and child health management information system, Birth Registry, introduced in Georgia in 2015 tracks maternal health and well-being during antenatal, delivery and postpartum period and reflects all potential factors for the timely detection of maternal and newborn health complications. The registry is a good instrument to strengthen the PHC in Georgia. However, clear framework and guidelines for the role of family doctors in preconception and postpartum care as well as adequate knowledge and skills will be required to detect and manage chronic diseases and other health risks, and better protect the health of women with non-communicable as well as communicable diseases and the health of their offspring. With noncommunicable diseases exemplifying the new and often ignored challenges that are emerging in women's health, policies and program must therefore address women's health holistically, from a life-course perspective, focusing on providing women with a continuum of care.

Finally, the health, social and economic shock caused by the COVID-19 pandemic has affected the lives and livelihoods of millions of people. However, the impact of Covid-19 pandemic for women and girls can be particularly devastating, further amplifying existing multiple disparities [212]. Beyond the adverse effects of Covid-19 disease on maternal and perinatal health, lockdowns, disruption of health-care services, and fear of attending health-care facilities might also have affected the wellbeing of pregnant women and their children

[213-214]. Studies have demonstrated decline of breast and cervical cancer screening tests, delays in cancer diagnoses and treatment, disproportionately affecting disadvantaged women [215-216]. The effect of disruption of health care services in Georgia during pandemic need to be carefully examined and effective strategy developed on mitigation of the long-term effects of the pandemic, including excess mortality risks from breast and cervical cancer. Making sure health systems take steps to identifying and dismantling the drivers of inequality must be at the heart of the recovery from COVID-19.

7. CONCLUSION AND IMPLICATIONS

This research presents the nationwide all-cause and cause-specific mortality patterns and trends over time among reproductive-aged women in Georgia for 2012. The thesis finds NCDs to be the greatest threat to women's health during their fertile years. Cancer is being the leading and breast cancer remaining the principal cause of premature mortality, while pregnancy-related conditions are at the ninth place among the top ten causes of death. Similarly, to many countries, Georgia will likely see a transition from mostly direct to more indirect causes of maternal deaths, stressing the urgent need to address NCDs and their effects on maternal health. These developments require reconceptualization of maternal health as part of the broader continuum of women's health. Strengthening prevention and efficient early diagnosis and treatment strategies and effective integration through sexual and reproductive and primary health care platforms will be required to better meet the challenge of women's cancer. Importantly, as Covid-19 is expected to have a particularly negative impact on women in the long term, effective strategy need to be developed to mitigate the long-term effects of the pandemic and to address the drivers of inequality in the pandemic recovery efforts.

A significant improvement in death registration coverage and an improvement in reporting maternal deaths as compared with previous, RAMOS08 findings demonstrate remarkable progress achieved by civil registration and vital statistics (CRVS) system in death registration completeness. Reforms including mandatory notification of a death within 5 days, electronic medical death certification, linkage of death records, and mandatory notification of maternal death to the Ministry of Labor, Health and Social Affairs (MOLHSA) within 24 hours were important changes implemented to strengthen maternal death identification and notification. However, inadequacies in quality of mortality data, completeness of ascertainment and

quality of coding will require undergraduate and post-graduate medical education and continuous trainings for physicians and coders in the cause-of-death certification and ICD coding practices. Periodic evaluations of medical death certificates samples and provision of feedback on quality of certification to health care professionals and facilities will help to improve the data quality. Moreover, practice of postmortem examination and autopsy in Georgia needs to be improved to aid health care providers determine the cause of death. Enhancing active surveillance to identify cases of maternal deaths, including late maternal deaths should be a focus, as well.

Further gains in maternal health outcomes across Georgia will require constant improvements in quality and safety at multiple levels of the health system. Among the maternal deaths, direct maternal causes comprised most of cases in our study, indicating that improvements of the quality of obstetric care is warranted. The cases of maternal mortality in our study illustrate the presence of gaps in quality such as delayed care and misdiagnoses, inadequate treatment, failure to follow national protocols and delays or inappropriate referrals to manage obstetric emergencies. Comprehensive, multi-dimensional, proactive strategies are of paramount importance to implement efforts to address these challenges and to minimize and hopefully eliminate preventable maternal deaths. Recommended actions include: (1) implementing confidential inquires and routine periodic national analyses and monitoring of maternal deaths, including examining maternal deaths through an equity lens by the maternal mortality review national committee with the summary of reviews made public; (2) establishing an internal (facility-based) clinical audit system to guide the design of obstetric interventions and policies; (3) strengthening preconception care and counselling for women of child-bearing age, especially for women with pre-existing medical conditions and once pregnant, monitoring by multidisciplinary teams; (4) improving antenatal care services to ensure evidence-based quality care and timely referral for complications; (5) expanding

policies and coverage for routine postpartum care focusing on early recognition of complications to reduce late maternal deaths; (6) addressing health workforce challenges through creating opportunities for and developing a system for effective continuous medical education as well as working conditions that support their well-being; (7) implementing quality improvement initiatives to address modifiable risk factors; and finally, (8) introducing mechanisms to reward quality and safety of maternity care, including financial incentives for measured quality of care and public reporting of healthcare quality data. Implementing comprehensive measures to stop and reverse the current steep rise in cesarean section rates is also necessary.

The major strides made over the last decade in Georgia to improve maternal care have had a real impact, when measured in the reduction of maternal deaths. Despite this progress, our research suggests that maternal health and survival need to remain on the public agenda and that eliminating the inequities that lead to disparities in quality and outcomes in maternal health must be a focus. Efficient reforms are needed to promote the human rights goal of ending preventable maternal deaths in Georgia.

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9.PAPERS

I

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ORIGINAL RESEARCH

Leading causes of death of women of reproductive age in the Republic of Georgia: findings from the National Reproductive Age Mortality Survey (2014)

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Purpose: An understanding of women's health problems during the reproductive years, based on reliable cause-of-death data, is of critical importance to avoid premature female mortality. This study aimed to investigate mortality levels, cause-specific patterns, and trends in women of reproductive age in Georgia.

Materials and methods: The National Reproductive Age Mortality Survey (2014) was conducted to identify all causes of death for women aged 15–49 years in 2012. The leading causes were compared with those in 2006, using directly age-standardized death rates (ASDRs). The accuracy of official cause-of-death data was assessed against verbal autopsy (VA) diagnoses, using kappa statistics, sensitivity, positive predictive value, and misclassification analyses.

Results: Of 913 eligible deaths, VAs were completed for 878 deaths. Noncommunicable diseases (NCDs) were the dominant causes of death (69.6% or 53.1/100,000), with cancer taking a major toll (45.2% or 34.5/100,000), followed by injuries (18.6% or 14.2/100,000). Breast cancer (12.5%), road injuries (9.1%), cervical cancer (6.5%), cerebrovascular diseases (5.2%), uterine cancer (4.1%), brain cancer (3.4%), suicide (3.1%), stomach cancer (3.0%), maternal disorders (2.6%), and liver cirrhosis (2.2%) contributed to the 10 leading specific causes of death, with the majority being substantially underreported in official statistics. This was primarily due to a significantly higher proportion (84%, $p<0.05$) of deaths routinely assigned ill-defined codes. Since 2006, statistically significant changes in ASDRs, with declines, were observed only for undetermined causes (40%, $p<0.05$) and ovarian cancer (54%, $p<0.05$); ovarian cancer and tuberculosis were replaced by stomach cancer and liver cirrhosis in the top 10 cause-of-death list.

Conclusion: NCDs continue to be the major health threats for Georgian women of reproductive age. The VA method proved a feasible tool to yield essential cause-of-death information for this population. Further research is needed to inform national health promotion and disease prevention interventions to be focused on NCDs and reproductive health needs with an integrated approach.

Keywords: women's health, mortality, verbal autopsy, noncommunicable diseases, injuries, cancer

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Introduction

A comprehensive approach to women's health from a life course perspective, going beyond the reproductive and maternal realm, provides a unique opportunity to address

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the whole spectrum of health risks and more effectively reduce premature female mortality.[1–3] Reproductive years (15–49 years) have a particular impact on women's health and well-being as this stage of life is associated with the double burden of child-bearing and a wide range of preventable health issues, faced by their male counterparts.[2,3] This has important implications for both present and future generations. There are also large variations across and within geographical regions. Young adult women in more developed settings tend to die predominantly from noncommunicable diseases (NCDs), whereas those in the least-developed settings are more likely to die from maternal causes and infectious diseases.[2,3] Over recent decades and at different rates, low- and middle-income countries (LMICs) have experienced epidemiologic transitions, which have shifted the disease burden from communicable to chronic NCDs.[2–6] Concurrently, there has been a substantial reduction in maternal deaths, which now account for only 6%–40% of all reproductive-aged female deaths in many of these countries.[2,3,7] There are persistent gaps in the knowledge of health problems among women of reproductive age in LMICs.[2,3,7] This is primarily owing to the lack of high-quality national-level cause-of-death data stemming from inadequate civil registration and vital statistics (CRVS) systems.[8] In the absence of complete CRVS, several alternative approaches, including reproductive age mortality surveys (RAMOSs) and verbal autopsies (VAs), have been increasingly recommended to yield useful information about population-level cause-of-death patterns and inform policy decisions.[9–11]

Georgia, one of the former Soviet Republics in the Caucasus Region of Eurasia, with an estimated population of four million, belongs to the World Bank lower middle-income country group and the World Health Organization (WHO) European Region.[12,13] Regardless of numerous political, economic, and social upheavals since independence in 1991, Georgia is currently undergoing rapid economic growth.[13,14]

As with other former Soviet bloc countries, Georgia continues to face the critical challenges of data quality,[8,15,16] notwithstanding recent meaningful reforms to improve its CRVS system.[17] This has been reflected in substantial inconsistencies between official statistics and the various survey findings supported by international agencies.[15,18] The first national RAMOS, conducted in Georgia in 2008 (RAMOS08) through the technical support of the US Centers for Disease Control and Prevention (CDC), revealed considerable discrepancies between these two sources in overall and cause-specific mortality patterns for women of reproductive age in 2006, highlighting the important gaps in both death registration coverage and cause-of-death ascertainment in the CRVS system.[19]

The poor accuracy and reliability of the official cause-of-death statistics and the need to identify mortality patterns and likely changes over time in this age group of Georgian women resulted in a repeat national RAMOS. The second national RAMOS was conducted in Georgia in 2014 (RAMOS14) by the National Center for Disease Control and Public Health (NCDC&PH) and replicated the methodology of the RAMOS08.[19] The primary aim of this study was to determine all causes of death in women aged 15–49 years who died in Georgia in 2012. The secondary aim was to investigate changes over time in all-cause and cause-specific mortality.

Materials and methods

Data collection and assigning causes of death

First, all eligible deaths were identified based on triangulation of mortality data for the year 2012 available from multiple sources. These included CRVS and NCDC&PH's mortality datasets, regional death registers, as well as hospital and ambulance service registers.

In the second phase, the VA interviews with family members or other caregivers of decedents were conducted from March to December 2014 by household visits within 24 months of death, considering the local cultural context for the mourning period. Detailed information on premortem illness signs and symptoms was collected by skilled female interviewers with a medical background using the VA instrument. This instrument was developed for the RAMOS08 and based on the CDC questionnaires for pregnancy mortality studies and surveillance systems, combined with the WHO international standard VA questionnaire.[19,20]

Completed VA questionnaires were reviewed blind by two physicians to assign the most probable underlying cause to each death according to the rules of the International Classification of Diseases, 10th revision (ICD-10).[21] Discrepancies in coding were resolved by a third physician who adjudicated the final diagnosis. The VA-derived maternal causes, based on the new ICD for Maternal Mortality (ICD-MM) definitions ("direct", "indirect", and "late" maternal deaths),[22] were further investigated through a hospital medical record review. They were finally confirmed by the multidisciplinary expert panel of physicians.

Tabulating causes of death and statistical analysis

The VA diagnoses were first compared with the CRVS diagnoses for the same deaths, aggregated into the WHO

General Mortality Tabulation List 1 of ICD-10 (hereafter referred to as WHO list)[23] and then into a shortened list of the most relevant causes.

Agreement of cause attribution between the two sources was assessed based on the Cohen's kappa (k) statistic, with the corresponding 95% CIs.[24] The strength of agreement was evaluated as poor for k=0.01–0.20, fair for k=0.21–0.40, moderate for k=0.41–0.60, good for k=0.61–0.80, and almost perfect for k=0.81–1.00.[24] Sensitivity and positive predictive value (PPV) of the CRVS system for each cause category were measured against VA diagnosis as a reference standard. Estimates of kappa, sensitivity, and PPV with the corresponding 95% CIs were computed by DAG_Stat spreadsheet.[25] Over- or underreporting of causes of death in CRVS were determined against the same reference standard based on Nam and Blackwelder method[26] by calculating the relative differences in mortality proportions for each cause category, with the corresponding 95% CIs, using NCSS 11 statistical software.[27] Patterns of misclassification between CRVS and VA diagnoses were further analyzed by cross-tabulating these two data based on the shortened WHO list.

Using the Global Burden of Disease (GBD) classification,[6] VA-based causes of death were further reclassified into three broad categories: communicable, maternal, neonatal, and nutritional disorders; NCDs; and injuries. In addition, the fourth group of undetermined causes incorporated all deaths assigned ill-defined and unknown codes.[11] Crude mortality rates (all-cause-, age- and cause-specific per 100,000 women) were calculated using the 5-year age groups (from 15–19 to 45–49 years) and the corresponding mid-year female population estimates as denominators obtained from official sources.[28] Age-standardized death rates (ASDRs) were then computed by applying age-specific death rates to the world standard population age distribution (2000–2025) using the direct method[29] and compared to those for the reference period of 2006.[19] The two populations were deemed significantly different in their ASDRs at the 0.05 level if the 95% CI of the standardized rate ratio (SRR) excluded 1. Both the ASDRs and the SRRs, with the corresponding 95% CIs, were calculated using Rothman's Episheet.[30]

All other statistical analyses in our study were performed using SPSS software version 21.0.[31]

Ethical approval and informed consent

Ethical approval for this study was received from the Institutional Review Board of the NCDC&PH and the Regional Committees for Medical and Health Research Ethics South East Norway. Written informed consent was obtained from all respondents prior to interviews.

Results

Of 913 identified eligible deaths, VAs were successfully completed for 878 deaths, which yielded a response rate of 96.2% and included two cases found to be unreported in official sources. Only one family refused to be interviewed, and 34 families could not be traced after their family member's death. The overall median age at death was 42 years (range 15–49 years), and over two-thirds of deaths (72.4%) occurred outside of health institutions.

Cause agreement and misclassification patterns

Table 1 summarizes the findings of the overall and individual-level agreement in attribution of causes of death between the CRVS and VA sources based on the shortened WHO list. The overall level of agreement on cause-of-death ascertainment between these two data was fair (k=0.36, 95% CI=0.33 to 0.40), showing a slight improvement from that when using the WHO list (k=0.34, 95% CI=0.31 to 0.38). Individual agreement was extremely poor for ill-defined causes and unspecified external causes, with the lowest kappa scores (0.04 and 0.06, respectively). Among specific causes of death, disagreement between the two sources was particularly evident for suicide, transport accidents, neurologic disorders, and liver diseases (k=0.12–0.20). By contrast, the level of agreement was good for respiratory tuberculosis (TB), breast cancer, leukemia, malignant skin melanoma, brain cancer, and maternal causes (k=0.63–0.75), and almost perfect (k=0.81) for stomach cancer (Table 1).

The observed sensitivity of the CRVS system relative to the VA in identifying the major specific causes of death was largely unsatisfactory (<50%), with the lowest values for suicide, transport accidents, liver diseases, neurologic disorders, uterine cancer, and diabetes (Table 1). Sensitivity was higher (>60%) for maternal causes and ovarian cancer, and the highest for stomach cancer (76.9%). The PPVs of the CRVS system, ranging from 5.4% to 100%, were among the lowest for liver disease, diabetes, and ischemic heart disease (IHD), while being the highest (100%) for transport accidents, brain cancer, maternal causes, and assault (Table 1).

The estimated degrees of over- and underdiagnosing for each cause category in CRVS due to misclassification are presented in Table 1. As shown, percentage changes for the majority of selected causes of death were statistically significant ($p<0.05$), with the largest differences seen for transport accidents, suicide, and uterine cancer compared to other specific causes (Table 1).

Table 2 provides the details of the misclassification patterns for the major causes of death using the shortened

Table 1 Comparison of civil registration and vital statistics and verbal autopsy causes of death based on the shortened WHO list for women of reproductive age: Georgia RAMOS 2014

Causes of death	CRVS		VA		Kappa (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	% change (95% CI)
	N	%	N	%				
Breast cancer	69	7.9	110	12.6	0.65 (0.56 to 0.73)	55.5 (45.7 to 64.9)	88.4 (78.4 to 94.9)	59.4[a] (35.7 to 91.2)
Transport accidents	7	0.8	82	9.4	0.14 (0.05 to 0.24)	8.5 (3.5 to 16.8)	100 (59.0 to 100)	1,071.4[a] (502.9 to 2,282.9)
Cervical cancer	31	3.5	57	6.5	0.52 (0.40 to 0.65)	42.1 (29.1 to 55.9)	77.4 (58.9 to 90.4)	83.9[a] (38.5 to 151.3)
Stroke	27	3.1	46	5.3	0.53 (0.39 to 0.67)	43.5 (28.9 to 58.9)	74.1 (53.7 to 88.9)	70.4[a] (25.0 to 139.1)
Remainder of malignant neoplasms	34	3.9	43	4.9	0.39 (0.25 to 0.53)	37.2 (23.0 to 53.3)	47.1 (29.8 to 64.9)	26.5 (–0.1 to 0.8)
Symptoms, signs, and abnormal clinical and laboratory findings	229	26.1	37	4.2	0.04 (0.00 to 0.09)	40.5 (24.8 to 57.9)	6.6 (3.7 to 10.6)	–83.8[a] (–87.7 to –76.9)
Uterine cancer	9	1.0	36	4.1	0.34 (0.17 to 0.52)	22.2 (10.1 to 39.2)	88.9 (51.8 to 99.7)	300.0[a] (134.1 to 637.5)
Brain cancer	16	1.8	30	3.4	0.69 (0.53 to 0.84)	53.3 (34.3 to 71.7)	100 (79.4 to 100)	87.5[a] (43.3 to 176.7)
Other heart diseases	53	6.1	29	3.3	0.26 (0.13 to 0.39)	41.4 (23.5 to 61.1)	22.6 (12.3 to 36.2)	–45.3[a] (–62.8 to –20.3)
Intentional self-harm	4	0.5	27	3.1	0.12 (–0.04 to 0.28)	7.4 (0.9 to 24.3)	50.0 (6.8 to 93.2)	575.0[a] (168.3 to 1,669.3)
Stomach cancer	23	2.6	26	3.0	0.81 (0.69 to 0.93)	76.9 (56.4 to 91.0)	87.0 (66.4 to 97.2)	13.0 (–12.8 to 50.2)
Pregnancy, childbirth, and the puerperium	14	1.6	23	2.6	0.75 (0.60 to 0.91)	60.9 (38.5 to 80.3)	100 (76.8 to 100)	64.3[a] (28.5 to 145.2)
Diseases of the nervous system	17	1.9	22	2.5	0.19 (0.02 to 0.36)	18.2 (5.2 to 40.3)	23.5 (6.8 to 49.9)	29.4 (–26.1 to 127.7)
All other external causes	92	10.5	19	2.2	0.06 (–0.02 to 0.13)	26.3 (9.1 to 51.2)	5.4 (1.8 to 12.2)	–79.4[a] (–87.1 to –67.2)
Remainder of diseases of the circulatory system	6	0.7	19	2.2	0.31 (0.08 to 0.55)	21.1 (6.1 to 45.6)	66.7 (22.3 to 95.7)	216.7[a] (54.7 to 591.1)
Ischemic heart diseases	19	2.2	17	1.9	0.38 (0.17 to 0.58)	41.2 (18.4 to 67.1)	36.8 (16.3 to 61.6)	–10.5 (–46.9 to 50.1)
Leukemia	11	1.3	16	1.8	0.66 (0.45 to 0.87)	56.3 (29.9 to 80.2)	81.8 (48.2 to 97.7)	45.5 (–7.2 to 141.6)
Ovarian cancer	21	2.4	15	1.7	0.60 (0.41 to 0.79)	73.3 (44.9 to 92.2)	52.4 (29.8 to 74.3)	–28.6 (–54.6 to 8.3)
Respiratory tuberculosis	8	0.9	14	1.6	0.63 (0.40 to 0.87)	50.0 (23.0 to 77.0)	87.5 (47.3 to 99.7)	75.0[a] (5.1 to 220.0)
Lung cancer	13	1.5	13	1.5	0.45 (0.21 to 0.69)	46.2 (19.2 to 74.9)	46.2 (19.2 to 74.9)	0.0 (–44.2 to 79.1)
Liver diseases	7	0.8	12	1.4	0.20 (–0.04 to 0.45)	16.7 (2.1 to 48.4)	28.6 (3.7 to 71.0)	71.4 (–23.9 to 292.1)
Colorectal cancer	7	0.8	12	1.4	0.52 (0.25 to 0.80)	41.7 (15.2 to 72.3)	71.4 (29.0 to 96.3)	71.4 (–9.7 to 245.5)
Skin cancer	7	0.8	11	1.3	0.66 (0.41 to 0.92)	54.5 (23.4 to 83.3)	85.7 (42.1 to 99.6)	57.1 (–10.3 to 199.3)
Diabetes mellitus	9	1.0	11	1.3	0.29 (0.03 to 0.56)	27.3 (6.0 to 61.0)	33.3 (7.5 to 70.1)	22.2 (–41.5 to 157.6)
Assault	4	0.5	11	1.3	0.53 (0.22 to 0.84)	36.4 (10.9 to 69.2)	100 (39.8 to 100)	175.0[a] (40.3 to 559.4)
All other	139	15.9	138	15.8	0.36 (0.28 to 0.44)	46.4 (37.9 to 55.1)	46.0 (37.6 to 54.7)	–0.72 (–16.5 to 18.1)
Total	876	100	876	100	0.36 (0.33 to 0.40)			

Note: [a]*p*-value<0.05.
Abbreviations: CRVS, civil registration and vital statistics; PPV, positive predictive value; RAMOS, reproductive age mortality survey; VA, verbal autopsy; WHO, World Health Organization.

WHO list. The overwhelming majority of deaths (214/229), ascertained by the CRVS system as ill-defined causes, were reclassified by the VA into a wide range of ICD cause categories. This was particularly evident for breast cancer (33/110), transport accidents (13/82), cervical cancer (15/57), cerebrovascular diseases (11/46), uterine cancer (11/36) and suicide (7/27), as well as brain cancer (5/30) and maternal causes (5/23). Further increases in these important causes, namely breast cancer (16/110), cervical cancer (18/57), uterine cancer (17/36), cerebrovascular diseases (15/46), and brain cancer (9/30), as well as maternal causes (4/23) and suicide (4/27), were observed after their reallocation from various specific or unspecified causes of death of CRVS data. Furthermore, over half of the deaths due to transport accidents (55/82) and suicide (14/27) and nearly one-quarter of those due to assault (3/11) from the VA source were originally attributed to the category of "all other external causes". Overall, this category was vastly miscoded (73/92) in the CRVS source (Table 2).

Broad causes of death

Table 3 summarizes the VA-based cause-specific mortality patterns of reproductive-aged women in Georgia in 2012 based on the GBD classification. The all-cause crude mortality rate was 76.2 per 100,000 (95% CI=71.3 to 81.4). Of the four broad categories of death, NCDs were by far the leading cause of death, accounting for over two-thirds of all deaths (69.6%) or 53.1 deaths per 100,000. Cancer accounted for almost half of all deaths (45.2%) or 34.5 per 100,000 and was the most common NCD-related cause and the principal cause of death. The second most common NCD-related cause was cardiovascular disease (CVD), contributing to 13.2% of

Table 2 Misclassification patterns for selected causes of death for women of reproductive age: Georgia, RAMOS 2014

Causes of death		Verbal autopsy																									Total
		Breast CA	Transport	Cervical CA	Stroke	Other CA	Ill-defined	Uterine CA	Brain CA	Other heart	Suicide	Stomach CA	Maternal	Nervous	Other external	Other CVD	IHD	Leukemia	Ovarian CA	Resp. TB	Lung CA	Liver disease	Colorectal CA	Skin CA	Diabetes	Assault	All other	
CRVS	Breast CA	**61**	0	0	0	1	1	3	0	0	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	**69**
	Transport	0	**7**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**7**
	Cervical CA	1	0	**24**	0	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**31**
	Stroke	1	0	0	**20**	0	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3	**27**
	Other CA	2	0	5	0	**16**	0	2	3	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	3	**34**
	Ill-defined	33	13	15	11	11	**15**	11	5	10	7	5	5	10	4	7	6	4	4	3	6	4	4	4	2	4	26	**229**
	Uterine CA	0	0	1	0	0	0	**8**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**9**
	Brain CA	0	0	0	0	0	0	0	**16**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**16**
	Other heart	0	0	2	3	1	7	0	1	**12**	0	0	1	0	1	4	3	0	0	3	0	0	0	0	2	0	13	**53**
	Suicide	0	0	0	0	0	0	0	0	0	**2**	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	**4**
	Stomach CA	1	0	0	0	0	0	0	0	0	0	**20**	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	**23**
	Maternal	0	0	0	0	0	0	0	0	0	0	0	**14**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**14**
	Nervous	1	0	0	3	1	0	0	2	0	1	0	0	**4**	1	0	0	0	0	0	0	0	0	0	0	0	4	**17**
	Other external	0	55	0	1	1	1	0	0	0	14	0	1	1	**5**	0	0	0	0	0	0	0	0	0	0	3	10	**92**
	Other CVD	0	0	0	0	0	1	0	0	0	0	0	0	0	0	**4**	0	0	0	0	0	0	0	0	1	0	0	**6**
	IHD	0	0	0	0	0	3	0	1	2	0	0	0	0	0	0	**7**	0	0	0	0	0	0	0	1	0	5	**19**
	Leukemia	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**9**	0	0	0	0	0	0	0	0	1	**11**
	Ovarian CA	0	0	2	0	1	0	5	0	0	0	0	0	0	0	1	0	0	**11**	0	0	0	0	0	0	0	1	**21**
	Resp. TB	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**7**	0	0	0	0	0	0	1	**8**
	Lung CA	1	0	2	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	**6**	0	0	1	0	0	0	**13**
	Liver disease	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**2**	0	0	0	0	4	**7**
	Colorectal CA	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**5**	0	0	0	0	**7**
	Skin CA	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**6**	0	0	0	**7**
	Diabetes	0	0	0	0	0	2	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	**3**	0	2	**9**
	Assault	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**4**	0	**4**
	All other	7	7	5	8	9	5	0	1	5	3	0	1	4	7	3	0	1	0	1	0	4	2	0	2	0	**64**	**139**
	Total	**110**	**82**	**57**	**46**	**43**	**37**	**36**	**30**	**29**	**27**	**26**	**23**	**22**	**19**	**19**	**17**	**16**	**15**	**14**	**13**	**12**	**12**	**11**	**11**	**11**	**138**	**876**

Notes: The values in bold font reflect total number of deaths attributed to each cause category by CVRS (raws) or verbal autopsy (columns), while the diagonal values in bold font reflect the number of death cases attributed to the same cause of death by both sources (cause agreement).

Abbreviations: CA, cancer; CRVS, civil registration and vital statistics; CVD, cardiovascular disease; IHD, ischemic heart disease; RAMOS, reproductive age mortality survey; Resp. TB, respiratory tuberculosis.

all deaths. Almost one-fifth (18.6%) of all deaths were due to injuries, accounting for 14.2 deaths per 100,000, making them the second leading broad category of death. This category was followed by communicable, maternal, neonatal, and nutritional disorders at 7.4% or 5.6 deaths per 100,000. Undetermined causes contributed to only 4.4% (Table 3).

The cause-of-death pattern varied across the age groups (Table 4). Injuries were the principal cause of death in women aged under 25 years, accounting for nearly half of all deaths in this age group and particularly affecting those aged 15–19 years (63.3%). By contrast, more than two-thirds of deaths in women aged ≥25 years were due to NCDs, making them the principal cause of death in this age category, with the greatest proportion in the oldest age group (84.0%). Cancer was the most common cause of NCD-related deaths across all age categories, being the principal cause of death in those aged ≥30 years and killing half of the women in this age group. CVD ranked as the third leading cause of death in the youngest age group after injuries and cancer, but the second in the oldest age group. Communicable, maternal, neonatal, and nutritional disorders were most prominent and the third top cause in the 20–24-year age group (24.5%), holding their rank in the 30–39-year age group, but ranking second in those aged 25–29 years after injuries and cancer. Undetermined causes at 5.3% were most pronounced in the oldest age group (Table 4).

Figure 1 shows a steady increase in crude mortality rates from all causes combined, NCDs, cancer, and CVD with age, in contrast to injuries and communicable, maternal, neonatal, and nutritional disorders.

Specific causes of death

Examining the specific causes of death, based on the GBD classification (Table 3), breast cancer was found to be the

Table 3 All-cause and cause-specific crude and age-standardized death rates (per 100,000) and standardized rate ratios for women of reproductive age by year: Georgia RAMOS 2008 and 2014

Causes of death	2006				2012				SRR (95% CI)
	% (N)	R (95% CI)	ASDR (95% CI)	Rank	% (N)	R (95% CI)	ASDR (95% CI)	Rank	
All causes	100 (918)	77.3 (72.4 to 82.4)	71.2 (66.5 to 75.8)		100 (878)	76.2 (71.3 to 81.4)	70.0 (65.3 to 74.7)		0.98 (0.90 to 1.08)
Communicable, maternal, neonatal, and nutritional disorders	8.4 (77)	6.5 (5.2 to 8.1)	6.6 (5.1 to 8.1)	4	7.4 (65)	5.6 (4.4 to 7.1)	5.4 (4.1 to 6.7)	3	0.82 (0.59 to 1.1)
Tuberculosis	2.9 (27)	2.3 (1.5 to 3.3)	2.3 (1.4 to 3.1)	8	1.9 (17)	1.5 (0.9 to 2.3)	1.4 (0.7 to 2.1)	11	0.62 (0.34 to 1.1)
Maternal disorders	3.3 (30)	2.5 (1.7 to 3.6)	2.7 (1.7 to 3.7)	5	2.6 (23)	2.0 (1.3 to 2.9)	2.0 (1.2 to 2.8)	9	0.73 (0.43 to 1.3)
Noncommunicable diseases	68.5 (629)	53.0 (49.0 to 57.2)	47.6 (43.8 to 51.3)	1	69.6 (611)	53.1 (49.0 to 57.4)	47.5 (43.7 to 51.3)	1	1.00 (0.89 to 1.12)
Neoplasms	45.1 (414)	34.9 (31.6 to 38.3)	31.3 (28.3 to 34.3)	1	45.2 (397)	34.5 (31.2 to 38.0)	30.9 (27.9 to 34.0)	1	0.99 (0.86 to 1.14)
Stomach cancer	2.1 (19)	1.6 (1.0 to 2.5)	1.4 (0.7 to 2.0)	14	3.0 (26)	2.3 (1.5 to 3.3)	2.0 (1.3 to 2.8)	8	1.50 (0.83 to 2.71)
Trachea, bronchus, and lung cancers	2.0 (18)	1.5 (0.9 to 2.3)	1.4 (0.7 to 2.1)	13	1.5 (13)	1.1 (0.6 to 1.9)	1.0 (0.5 to 1.6)	15	0.72 (0.35 to 1.47)
Breast cancer	14.6 (134)	11.3 (9.5 to 13.3)	10.0 (8.3 to 11.6)	1	12.5 (110)	9.6 (7.9 to 11.5)	8.5 (6.9 to 10.1)	1	0.86 (0.66 to 1.10)
Cervical cancer	5.7 (52)	4.4 (3.3 to 5.7)	3.9 (2.8 to 5.0)	4	6.5 (57)	4.9 (3.8 to 6.4)	4.4 (3.2 to 5.5)	3	1.12 (0.77 to 1.64)
Uterine cancer	3.6 (33)	2.8 (1.9 to 3.9)	2.5 (1.6 to 3.3)	6	4.1 (36)	3.1 (2.2 to 4.3)	2.8 (1.9 to 3.7)	5	1.12 (0.70 to 1.81)
Colon and rectum cancers	1.1 (10)	0.8 (0.4 to 1.5)	0.7 (0.3 to 1.2)	18	1.4 (12)	1.0 (0.6 to 1.8)	0.9 (0.4 to 1.5)	17	1.28 (0.55 to 2.97)
Malignant melanoma of skin	0.8 (7)	0.6 (0.3 to 1.2)	0.6 (0.1 to 1.0)	19	1.3 (11)	1.0 (0.5 to 1.7)	0.9 (0.4 to 1.4)	18	1.57 (0.60 to 4.08)
Ovarian cancer	3.5 (32)	2.7 (1.9 to 3.8)	2.5 (1.6 to 3.3)	7	1.7 (15)	1.3 (0.8 to 2.1)	1.1 (0.5 to 1.7)	13	0.46[a] (0.25 to 0.85)
Brain and nervous system cancers	2.7 (25)	2.1 (1.4 to 3.1)	1.9 (1.2 to 2.7)	10	3.4 (30)	2.6 (1.8 to 3.7)	2.4 (1.5 to 3.2)	6	1.22 (0.71 to 2.08)
Leukemia	2.3 (21)	1.8 (1.1 to 2.7)	1.8 (1.0 to 2.5)	11	1.8 (16)	1.4 (0.8 to 2.2)	1.3 (0.7 to 2.0)	12	0.74 (0.38 to 1.42)
Cardiovascular and circulatory disorders	11.5 (106)	8.9 (7.3 to 10.8)	7.8 (6.3 to 9.3)	2	13.2 (116)	10.1 (8.4 to 12.0)	8.8 (7.2 to 10.4)	2	1.14 (0.87 to 1.48)
Ischemic heart disease	1.6 (15)	1.3 (0.7 to 2.0)	1.1 (0.5 to 1.7)	15	1.9 (17)	1.5 (0.9 to 2.3)	1.1 (0.5 to 2.2)	14	1.10 (0.55 to 2.22)
Cerebrovascular disease	6.2 (57)	4.8 (3.7 to 6.2)	4.1 (3.1 to 5.2)	3	5.2 (46)	4.0 (3.0 to 5.3)	3.5 (2.5 to 4.5)	4	0.84 (0.57 to 1.25)
Chronic respiratory diseases	1.0 (9)	0.8 (0.4 to 1.4)	0.7 (0.2 to 1.2)	6	0.6 (5)	0.4 (0.2 to 1.0)	0.4 (0.0 to 0.7)	6	0.54 (0.18 to 1.62)
Cirrhosis of the liver	2.0 (18)	1.5 (0.9 to 2.3)	1.4 (0.8 to 2.1)	12	2.2 (19)	1.6 (1.0 to 2.5)	1.4 (0.8 to 2.1)	10	1.01 (0.53 to 1.93)
Digestive diseases	1.5 (14)	1.2 (0.7 to 1.9)	1.0 (0.5 to 1.5)	5	0.9 (8)	0.7 (0.3 to 1.3)	0.6 (0.2 to 1.0)	5	0.59 (0.25 to 1.41)
Neurological disorders	1.6 (15)	1.3 (0.7 to 2.0)	1.3 (0.6 to 1.9)	4	2.4 (21)	1.8 (1.2 to 2.7)	1.7 (1.0 to 2.5)	4	1.36 (0.70 to 2.64)
Diabetes, urogenital, blood, and endocrine diseases	3.5 (32)	2.7 (1.9 to 3.8)	2.5 (1.7 to 3.4)	3	3.4 (30)	2.6 (1.9 to 3.7)	2.4 (1.5 to 3.3)	3	0.94 (0.57 to 1.56)
Diabetes mellitus	1.4 (13)	1.1 (0.6 to 1.8)	1.0 (0.4 to 1.5)	17	1.3 (11)	1.0 (0.5 to 1.7)	0.8 (0.3 to 1.3)	19	0.85 (0.38 to 1.90)
Injuries	15.9 (146)	12.3 (10.4 to 14.4)	12.0 (10.0 to 13.9)	2	18.6 (163)	14.2 (12.1 to 16.5)	14.1 (11.9 to 16.3)	2	1.17 (0.94 to 1.47)
Road injury	8.5 (78)	6.6 (5.2 to 8.2)	6.5 (5.0 to 7.9)	2	9.1 (80)	6.9 (5.5 to 8.6)	6.9 (5.4 to 8.5)	2	1.07 (0.78 to 1.47)
Self-harm and interpersonal violence	4.0 (37)	3.1 (2.2 to 4.2)	3.0 (2.0 to 4.0)		4.3 (38)	3.3 (2.4 to 4.5)	3.3 (2.2 to 4.3)		1.09 (0.69 to 1.72)
Self-harm	2.6 (24)	2.0 (1.3 to 3.0)	1.9 (1.2 to 2.7)	9	3.1 (27)	2.3 (1.6 to 3.4)	2.3 (1.4 to 3.2)	7	1.20 (0.69 to 2.09)
Interpersonal violence	1.4 (13)	1.1 (0.6 to 1.8)	1.1 (0.5 to 1.7)	16	1.3 (11)	1.0 (0.5 to 1.7)	0.9 (0.5 to 1.4)	16	0.88 (0.39 to 1.98)
Undetermined	7.2 (66)	5.6 (4.3 to 7.0)	5.0 (3.8 to 6.3)	3	4.4 (39)	3.4 (2.4 to 4.6)	3.0 (2.1 to 4.0)	4	0.60[a] (0.40 to 0.90)

Note: [a]p-value<0.05.
Abbreviations: ASDR, age-standardized death rate; R, crude death rate; RAMOS, reproductive age mortality surveys; SRR, standardized rate ratio.

number one cause in women aged 15–49 years, accounting for 12.5% of all deaths or 9.6 per 100,000, followed by road injuries at 9.1% or 6.9 per 100,000 and cervical cancer at 6.5% or 4.9 per 100,000. Cerebrovascular diseases were the fourth major cause (5.2%), whereas uterine cancer was the fifth (4.1%). Brain cancer (3.4%), with subsequent suicide (3.1%) ranked as the sixth and seventh leading causes of death, respectively, followed, in descending order, by stomach cancer, maternal disorders, and liver cirrhosis as the eighth, ninth, and tenth leading causes of death. TB at 1.9% or 1.5 per 100,000 was the most common cause of death from communicable diseases (Table 3).

A detailed analysis of specific causes of death by age categories (Table 4) identified road injuries as the principal cause of death in women aged under 35 years, killing nearly one-third (30.0%) of adolescent girls aged 15–19 years. Suicide ranked second ahead of cerebrovascular diseases in the youngest age group, but third in those aged 20–24 years behind maternal disorders, with the latter dropping down to the third place in the 25–34-year age group and further in the older groups, while not affecting those in the youngest and oldest age categories. Breast cancer was the second major cause of death in women aged 25–34 years, but the principal cause in the older age groups (35–49 years), followed by cervical cancer and road injuries in those aged 35–44 years, with cervical cancer being outranked by the second most common cerebrovascular diseases in the oldest age group. TB and brain cancer shared the third place with equally important maternal disorders in the 25–29-year age group, whereas stomach cancer was the third major cause in those aged 34–39 years. Becoming increasingly relevant with age, uterine and ovarian cancers were most prominent in the oldest age group, as were liver cirrhosis, IHD, and diabetes (Table 4).

Figure 2 illustrates the sharp increase with age in mortality rates for all five cancer-related deaths, cerebrovascular diseases, and liver cirrhosis, as opposed to mortality rates for road injuries, suicide, and maternal disorders, remaining relatively stable or decreasing with age.

Comparison of the leading causes of death in 2006 and 2012

Table 3 presents a comparison of mortality estimates for the leading causes of death of Georgian women of reproductive age between 2006 and 2012, based on the two national RAMOS (RAMOS08 and RAMOS14) findings. The all-cause ASDR per 100,000 women was 70.0 in 2012, showing no statistically significant difference from 71.2 in 2006 (SRR=0.98, 95% CI=0.90 to 1.08; $p>0.05$). Almost no statistically significant changes have been identified during that period in ASDRs for the broad categories of death either, including NCD broad subgroups, except for a statistically significant decline (SRR=0.60, 95% CI=0.40 to 0.90; $p<0.05$) seen in undetermined causes, making them rank down to the fourth place compared to 2006 (Table 3).

Likewise, among the major specific causes of death, statistically significant difference in the ASDR between 2 years was identified only for ovarian cancer, which more than halved (SRR=0.46, 95% CI=0.25 to 0.85; $p<0.05$) compared to 2006 (Table 3). Further changes during that period were observed in both composition and rankings of the 10 leading specific causes of death, with only breast cancer and subsequent road injuries maintaining their dominant positions. Specifically, ovarian cancer and TB, ranking seventh and eighth in 2006, were no longer apparent in the list of top 10 causes in 2012, being replaced by stomach cancer and liver cirrhosis, which moved up from their 14th and 12th places to the eighth and tenth, respectively. Beyond this, a rank increase was observed for cervical, uterine, and brain cancers, and suicide from their fourth, sixth, tenth, and ninth to the third, fifth, sixth, and seventh places, respectively, as opposed to a rank decrease for cerebrovascular diseases and maternal disorders from their third and fifth to the fourth and ninth places, respectively (Table 4).

Discussion

This paper presents the nationwide all-cause and cause-specific mortality patterns among women of reproductive age in Georgia for 2012 and trends over time based on the repeat national RAMOS findings. The all-cause crude mortality rate was 76.2 per 100,000. NCDs were the leading broad cause of death, accounting for 69.6% of all deaths or 53.1 per 100,000, whereas breast cancer was the number one specific cause of death, responsible for 12.5% of all deaths or 9.6 per 100,000.

Using multiple sources of mortality data, our study identified only two (0.2%) unregistered deaths in the 2012 official statistics. Compared to the RAMOS08 findings (25% in 2006),[19] this suggests a substantial improvement in death registration coverage in Georgia (98% according to the WHO).[12] This is most likely owing to the previously mentioned reforms in the CRVS system, which lawfully obliged all medical establishments and other responsible bodies to complete electronic birth and death certificates and submit by a set deadline to the Civil Registry Agency.[17] However, in line with the RAMOS08,[19] there were considerable discrepancies between the VA and CRVS in the underlying patterns of

Table 4 Cause-specific and age-specific mortality estimates for women of reproductive age: Georgia RAMOS 2014

Causes of death	Age					
	15–19 years		20–24 years		25–29 years	
	% (N)	R/100,000 (95% CI)	% (N)	R/100,000 (95% CI)	% (N)	R/100,000 (95% CI)
Communicable, maternal, neonatal, and nutritional disorders	3.3 (1)	0.7 (0.1 to 3.3)	24.5 (12)	6.6 (3.6 to 11.2)	14.0 (8)	4.5 (2.1 to 8.5)
Tuberculosis	0.0 (0)	0.0 (0.0 to 0.0)	6.1 (3)	1.6 (0.5 to 4.4)	5.3 (3)	1.7 (0.5 to 4.5)
Maternal disorders	0.0 (0)	0.0 (0.0 to 0.0)	16.3 (8)	4.4 (2.1 to 8.3)	5.3 (3)	1.7 (0.5 to 4.5)
Noncommunicable diseases	33.3 (10)	7.0 (3.6 to 12.5)	26.5 (13)	7.1 (4.0 to 11.9)	49.1 (28)	15.7 (10.7 to 22.4)
Neoplasms	13.3 (4)	2.8 (0.9 to 6.7)	20.4 (10)	5.5 (2.8 to 9.8)	33.3 (19)	10.7 (6.6 to 16.3)
Stomach cancer	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	3.5 (2)	1.1 (0.2 to 3.6)
Trachea, bronchus, and lung cancers	0.0 (0)	0.0 (0.0 to 0.0)	2.0 (1)	0.5 (0.0 to 2.6)	0.0 (0)	0.0 (0.0 to 0.0)
Breast cancer	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	7.0 (4)	2.2 (0.8 to 5.3)
Cervical cancer	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Uterine cancer	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	1.8 (1)	0.6 (0.5 to 4.5)
Colon and rectum cancers	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	3.5 (2)	1.1 (0.2 to 3.6)
Malignant melanoma of skin	0.0 (0)	0.0 (0.0 to 0.0)	4.1 (2)	1.1 (0.2 to 3.5)	1.8 (1)	0.6 (0.1 to 2.6)
Ovarian cancer	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Brain and nervous system cancers	3.3 (1)	0.7 (0.1 to 3.3)	0.0 (0)	0.0 (0.0 to 0.0)	5.3 (3)	1.7 (0.5 to 4.5)
Leukemia	3.3 (1)	0.7 (0.1 to 3.3)	2.0 (1)	0.5 (0.0 to 2.6)	7.0 (4)	2.2 (0.8 to 5.3)
Cardiovascular and circulatory disorders	10.0 (3)	2.1 (0.6 to 5.6)	4.1 (2)	1.1 (0.2 to 3.5)	8.8 (5)	2.8 (1.1 to 6.1)
Ischemic heart disease	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Cerebrovascular disease	6.7 (2)	1.4 (0.3 to 4.5)	2.0 (1)	0.5 (0.0 to 2.6)	0.0 (0)	0.0 (0.0 to 0.0)
Chronic respiratory diseases	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	1.8 (1)	0.6 (0.1 to 2.6)
Cirrhosis of the liver	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Digestive diseases	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Neurological disorders	3.3 (1)	0.7 (0.1 to 3.3)	0.0 (0)	0.0 (0.0 to 0.0)	3.5 (2)	1.1 (0.2 to 3.6)
Diabetes, urogenital, blood, and endocrine diseases	6.7 (2)	1.4 (0.3 to 4.5)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Diabetes mellitus	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)
Injuries	63.3 (19)	13.4 (8.3 to 20.5)	46.9 (23)	12.6 (8.2 to 18.6)	33.3 (19)	10.7 (6.6 to 16.3)
Road injury	30.0 (9)	6.3 (3.1 to 11.6)	24.5 (12)	6.6 (3.6 to 11.2)	21.1 (12)	6.7 (3.7 to 11.4)
Self-harm and interpersonal violence	13.3 (4)	2.8 (0.9 to 6.7)	16.3 (8)	4.4 (2.1 to 8.3)	3.5 (2)	1.1 (0.2 to 3.6)
Self-harm	10 (3)	2.1 (0.6 to 5.6)	10.2 (5)	2.7 (1.0 to 6.0)	1.8 (1)	0.6 (0.1 to 2.6)
Interpersonal violence	3.3 (1)	0.7 (0.1 to 3.3)	6.1 (3)	1.6 (0.5 to 4.4)	1.8 (1)	0.6 (0.1 to 2.6)
Undetermined	0.0 (0)	0.0 (0.0 to 0.0)	2.0 (1)	0.5 (0.0 to 2.6)	3.5 (2)	1.1 (0.2 to 3.6)
Total	100 (30)	21.1 (14.5 to 29.7)	100 (49)	26.9 (25.8 to 45.2)	100 (57)	32.0 (30.7 to 51.6)

Abbreviations: R, age-specific death rate; RAMOS, reproductive age mortality survey.

causes of death for this population in 2012, revealing significant underrepresentation of a clear majority of important cancer, injury, and maternal deaths in official sources, with transport accidents, suicide, and uterine cancer misrepresented as the leading specific causes of death. Showing overall fair agreement between two sources (k=0.36, 95% CI=0.33 to 0.40), along with largely unsatisfactory sensitivity (<50%) of the CVRS system in identifying the major specific causes of death, our study found the poor level of individual agreement (k<0.21) and the lowest values of sensitivity (≤22.2%) for these latter causes. Further analysis of the misclassification patterns revealed significant over reporting of ill-defined (84%, $p<0.05$) and unspecified external causes (79%, $p<0.05$) in the CRVS system as compared to only about 4% and 2% of these deaths, respectively, in VA data. A massive reallocation of the specific causes of death from ill-defined and further from various originally miscoded specific or "other" unspecified cause categories resulted in significant proportional increases in estimated mortality notably from breast, cervical, uterine, and brain cancers; cerebrovascular diseases; and maternal disorders, in addition to transport accidents and suicide (Table 1). Given the clear majority of deaths (72%) in our study sample occurred outside of health institutions, this observation suggests the failure of the system to collect cause-

30–34 years		35–39 years		40–44 years		45–49 years	
% (N)	R/100,000 (95% CI)	% (N)	R/100,000 (95% CI)	% (N)	R/100,000 (95% CI)	% (N)	R/100,000 (95% CI)
15.7 (13)	7.8 (4.4 to 13.0)	7.8 (10)	6.3 (3.2 to 11.1)	4.7 (9)	5.7 (2.8 to 10.5)	3.5 (12)	7.2 (3.9 to 12.2)
2.4 (2)	1.2 (0.2 to 3.9)	2.3 (3)	1.9 (0.5 to 5.0)	2.1 (4)	2.6 (0.9 to 6.1)	0.6 (2)	1.2 (0.2 to 3.8)
6.0 (5)	3.0 (1.1 to 6.6)	3.1 (4)	2.5 (0.8 to 6.0)	1.6 (3)	1.9 (0.5 to 5.1)	0.0 (0)	0.0 (0.0 to 0.0)
54.2 (45)	27.1 (20.0 to 35.9)	67.2 (86)	53.8 (43.3 to 66.1)	74.9 (143)	91.2 (77.2 to 107.1)	84.1 (286)	171.6 (152.5 to 192.3)
33.7 (28)	16.9 (11.4 to 24.0)	46.1 (59)	36.9 (28.4 to 47.3)	53.4 (102)	65.1 (53.3 to 78.6)	51.5 (175)	105.0 (90.3 to 121.4)
1.2 (1)	0.6 (0.1 to 2.8)	6.3 (8)	5.0 (2.4 to 9.4)	2.6 (5)	3.2 (1.2 to 7.0)	2.9 (10)	6.0 (3.1 to 10.6)
0.0 (0)	0.0 (0.0 to 0.0)	2.3 (3)	1.9 (0.5 to 5.0)	1.6 (3)	1.9 (0.5 to 5.1)	1.8 (6)	3.6 (1.5 to 7.4)
9.6 (8)	4.8 (2.3 to 9.1)	9.4 (12)	7.5 (4.1 to 12.7)	20.9 (40)	25.5 (18.5 to 34.4)	13.5 (46)	27.6 (20.5 to 36.5)
2.4 (2)	1.2 (0.2 to 3.9)	8.6 (11)	6.9 (3.7 to 11.9)	8.9 (17)	10.8 (6.6 to 17.0)	7.9 (27)	16.2 (10.9 to 23.2)
3.6 (3)	1.8 (0.5 to 4.8)	4.7 (6)	3.8 (1.6 to 7.7)	4.2 (8)	5.1 (2.4 to 9.6)	5.3 (18)	10.8 (6.6 to 16.7)
0.0 (0)	0.0 (0.0 to 0.0)	2.3 (3)	1.9 (0.5 to 5.0)	1.0 (2)	1.3 (0.3 to 4.1)	1.5 (5)	3.0 (1.1 to 6.6)
0.0 (0)	0.0 (0.0 to 0.0)	0.8 (1)	0.6 (0.1 to 2.9)	1.6 (3)	1.9 (0.5 to 5.1)	1.2 (4)	2.4 (0.8 to 5.7)
1.2 (1)	0.6 (0.1 to 2.8)	0.0 (0)	0.0 (0.0 to 0.0)	2.1 (4)	2.6 (0.9 to 6.1)	2.9 (10)	6.0 (3.1 to 10.6)
3.6 (3)	1.8 (0.5 to 4.8)	4.7 (6)	3.8 (1.6 to 7.7)	1.0 (2)	1.3 (0.3 to 4.1)	4.4 (15)	9.0 (5.3 to 14.5)
1.2 (1)	0.6 (0.1 to 2.8)	1.6 (2)	1.3 (0.2 to 4.0)	1.0 (2)	1.3 (0.3 to 4.1)	1.5 (5)	3.0 (1.1 to 6.6)
8.4 (7)	4.2 (1.9 to 8.3)	6.3 (8)	5.0 (2.4 to 9.4)	10.5 (20)	12.8 (8.0 to 19.3)	20.9 (71)	42.6 (33.5 to 53.4)
0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	1.0 (2)	1.3 (0.3 to 4.1)	4.4 (15)	9.0 (5.3 to 14.5)
4.8 (4)	2.4 (0.8 to 5.7)	0.8 (1)	0.6 (0.1 to 2.9)	4.2 (8)	5.1 (2.4 to 9.6)	8.8 (30)	18.0 (12.4 to 25.3)
0.0 (0)	0.0 (0.0 to 0.0)	0.0 (0)	0.0 (0.0 to 0.0)	0.5 (1)	0.6 (0.1 to 3.0)	0.9 (3)	1.8 (0.5 to 4.8)
2.4 (2)	1.2 (0.2 to 3.9)	0.8 (1)	0.6 (0.1 to 2.9)	2.6 (5)	3.2 (1.2 to 7.0)	3.2 (11)	6.6 (3.5 to 11.4)
0.0 (0)	0.0 (0.0 to 0.0)	0.8 (1)	0.6 (0.1 to 2.9)	1.0 (2)	1.3 (0.3 to 4.1)	1.5 (5)	3.0 (1.1 to 6.6)
1.2 (1)	0.6 (0.1 to 2.8)	5.5 (7)	4.4 (2.0 to 8.6)	2.6 (5)	3.2 (1.2 to 7.0)	1.5 (5)	3.0 (1.1 to 6.6)
4.8 (4)	2.4 (0.8 to 5.7)	3.9 (5)	3.1 (1.2 to 6.9)	2.6 (5)	3.2 (1.2 to 7.0)	4.1 (14)	8.4 (4.8 to 13.7)
1.2 (1)	0.6 (0.1 to 2.8)	1.6 (2)	1.3 (0.2 to 4.0)	1.0 (2)	1.3 (0.3 to 4.1)	1.8 (6)	3.6 (1.5 to 7.4)
25.3 (21)	12.6 (8.1 to 19.0)	21.1 (27)	16.9 (11.4 to 24.2)	15.7 (30)	19.1 (13.2 to 26.9)	7.1 (24)	14.4 (9.5 to 21.1)
15.7 (13)	7.8 (4.4 to 13.0)	8.6 (11)	6.9 (3.7 to 11.9)	6.3 (12)	7.7 (4.2 to 13.0)	3.2 (11)	6.6 (3.5 to 11.4)
4.8 (4)	2.4 (0.8 to 5.7)	6.3 (8)	5.0 (2.4 to 9.4)	3.7 (7)	4.5 (2.0 to 8.8)	1.5 (5)	3.0 (1.1 to 6.6)
2.4 (2)	1.2 (0.2 to 3.9)	5.5 (7)	4.4 (2.0 to 8.6)	3.1 (6)	3.8 (1.6 to 7.9)	0.9 (3)	1.8 (0.5 to 4.8)
2.4 (2)	1.2 (0.2 to 3.9)	0.8 (1)	0.6 (0.1 to 2.9)	0.5 (1)	0.6 (0.1 to 3.0)	0.6 (2)	1.2 (0.2 to 3.8)
4.8 (4)	2.4 (0.8 to 5.7)	3.9 (5)	3.1 (1.2 to 6.9)	4.7 (9)	5.7 (2.8 to 10.5)	5.3 (18)	10.8 (6.6 to 16.7)
100 (83)	50.0 (46.9 to 72.1)	100 (128)	80.1 (75.5 to 106.8)	100 (191)	121.8 (116.4 to 154.6)	100 (340)	204.0 (215.0 to 265.9)

of-death data on out-of-hospital deaths in Georgia. Overall, our findings are consistent with the recent global assessment of the national CRVS systems for the period of 1980–2012, classifying Georgia in the medium group of countries with inadequate quality of mortality data making it less useful for policy and research.[16] The excessive use of ill-defined and "other" unspecified codes particularly for external causes, cancers, and CVDs, in addition to systematic undercounting of maternal causes in the routine registration system, was also documented in earlier studies conducted in other former Soviet Republics and was largely attributed to artifacts in cause-of-death certification and coding practices.[8,15,16,32–34] Our study, therefore, signifies the need for continued trainings for physicians and coders in these important procedures,[32] as well as periodic assessments of the quality of routine mortality statistics, using VA as the best and reliable approach to improve national and regional cause-of-death data, particularly for deaths occurring without medical attention, in order to inform public health priorities.[8–11,35–37]

Based on the GBD classification, our study identified that NCDs, accounting for two-thirds of all deaths, were by far the leading causes of death in women during their child-bearing years in 2012, followed by injuries and communicable, maternal, neonatal, and nutritional causes. Breast cancer,

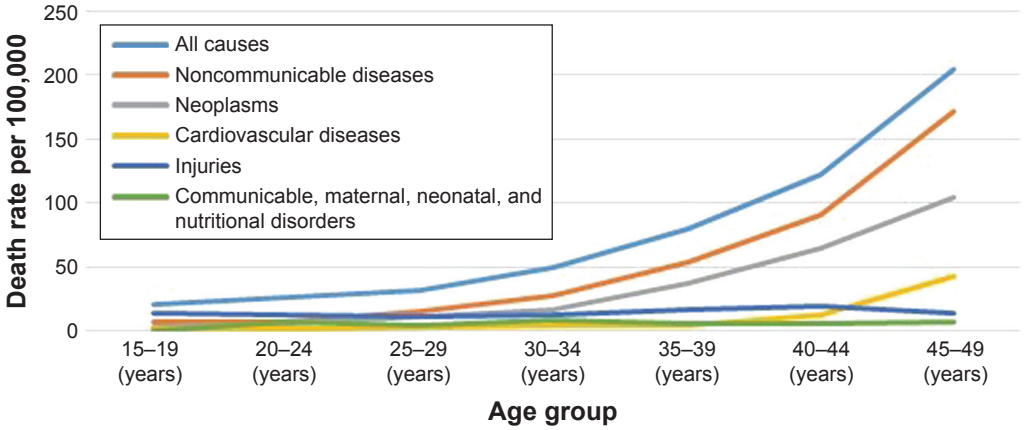

Figure 1 All-cause and cause-specific death rates by broad cause category and age group for women of reproductive age: Georgia, RAMOS 2014.
Abbreviation: RAMOS, reproductive age mortality survey.

followed by road injuries, cervical cancer, cerebrovascular diseases, uterine cancer, brain cancer, suicide, stomach cancer, maternal disorders, and liver cirrhosis, contributed to the 10 leading specific causes of death. Overall, the mortality level and cause-of-death patterns have remained fairly consistent over the 6-year period. A comparison of all-cause and cause-specific ASDRs with those in 2006 revealed statistically significant changes, with declines, only for undetermined causes (40%, $p<0.05$) and ovarian cancer (54%, $p<0.05$). While the reduction in ill-defined causes may partly be attributable to improved skills of field interviewers and death certifiers since the RAMOS08,[19] the downward trend in ovarian cancer mortality is in line with that observed globally and in Europe, including in certain former Soviet Republics, between 2002 and 2012.[38] Declines were systematically larger in the young (20–49 years) and mainly linked to oral contraceptives' use and their protective effects against this cancer.[38] However, this cannot fully explain such a dramatic reduction in this cancer mortality in Georgia, given the very low prevalence (4%) of the oral contraceptives' use among women aged 15–44 years, despite a twofold increase between 1999 and 2010, as documented by the Georgia Reproductive Health Survey 2010.[17] Therefore, this requires further research. Besides this, dropping in rank, ovarian cancer, along with TB, was no longer evident in the top 10 cause list in 2012, being replaced by more important stomach cancer and liver cirrhosis. Rank declines due to relative decreases in absolute numbers of deaths were seen for cerebrovascular diseases and maternal disorders, with rank increases for cervical, uterine, and brain cancers.

An observed decline, though nonsignificant, in deaths from communicable, maternal, neonatal, and nutritional disorders, and the persistent predominance of NCD causes are in line with the global shift of causal patterns of mortality in reproductive-aged women, including in LMICs.[1–3,6] The rapid rise in overall premature deaths from NCDs (48%),

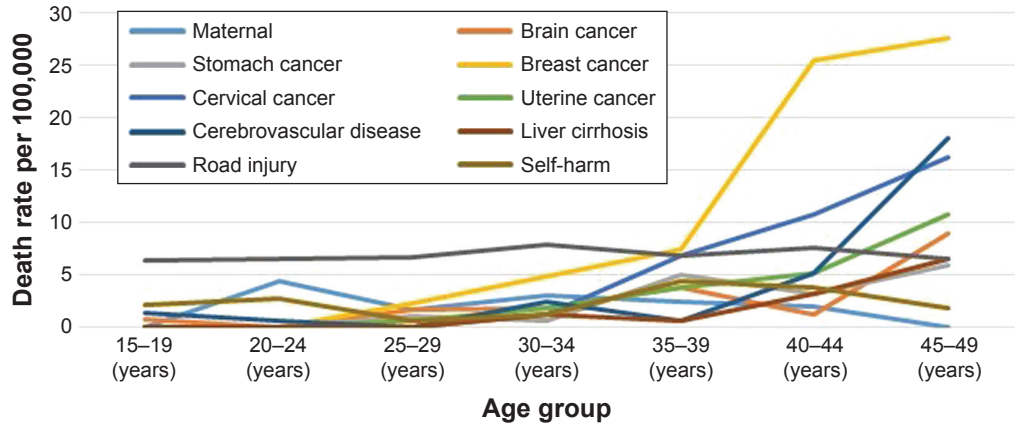

Figure 2 Cause-specific death rates by specific cause category and age group for women of reproductive age: Georgia, RAMOS 2014.
Abbreviation: RAMOS, reproductive age mortality survey.

largely from CVD and cancer in these countries, is closely linked to the modernization and urbanization during the socioeconomic transition, resulting in a wider adoption of more affluent lifestyle choices, such as unhealthy diet, low physical activity, smoking, and alcohol use, with associated changes in body mass index and lipid and blood pressure profiles.[2–6,13,39–41] While Georgia is challenged by overall 93% of NCD mortality, of which 19% occur in women under age 70, over half (54.2%) of adult female population aged ≥18 years are overweight and more likely to be obese than man (28.5% vs 21.8%), 22.3% show insufficient physical activity, whereas 31.7% has the raised blood pressure,[39,42,43] mirroring the global and the WHO European Regional trends.[13,39,41] There is also evidence of the increasing tobacco epidemic in Georgian women, particularly in those aged under 40 years, being more educated and living in urban areas, similar to other former Soviet Republics.[44] However, in view of the current demographic trends of increasing life expectancy and decreasing fertility, along with the rapid socioeconomic development in Georgia,[12,14,18,40,41] further country-specific research is needed to identify expected changes in risk and disease patterns in this population in order to ensure evidence-informed and targeted national disease prevention and control interventions.

A particularly alarming finding of our study pertains to cancer-related causes of death, remaining dominant and contributing to almost half of all eligible deaths. Breast and reproductive system cancers collectively were responsible for one-quarter of all deaths. Our findings are in line with global estimates, ranking breast and cervical cancers among the leading causes of death in reproductive-aged women, including in the WHO European Region.[6,41] Breast cancer is the major cause of death in young adult women in Central and Western Europe, ranking fourth in Central Asia, whereas cervical cancer ranks fourth in Central Europe.[41] Over the past three decades, worldwide deaths from breast and cervical cancers in this age group increased 1.8% and 0.45% per year, respectively, with both cancers combined currently causing more deaths than maternal causes in general.[45,46] As breast and cervical cancers now kill more women than any other forms of cancer in all parts of the developing world, both incidence and mortality from each type of cancer in women of reproductive age are substantially higher than in developed countries, with breast cancer predominance.[38,45,46] The observed trends in breast and cervical cancer mortality have been attributed to women's sexual and reproductive choices and other exposures in early life, such as lower parity and later age at first birth, breastfeeding history, obesity and low physical activity, history of infection with the human papillomavirus (HPV), and various occupational factors, coupled with the limited awareness of and access to disease prevention and treatment services in low-recourse settings.[3,41,46,47] Previous research in Russia and Ukraine documented a steady increase in breast cancer incidence and mortality over the past few decades that has been linked to the very low contemporary birth rate in both countries.[48] The other studies highlighted higher incidence and mortality rates of cervical cancer across the former Soviet Republics than in most Western European countries, which have been explained by opportunistic screening programs, lack of efficient call–recall systems, low coverage, and the absence of quality-assured cytology with centralized screening registry, alongside low HPV vaccine uptake.[49,50] One study from Georgia indicated a relatively high prevalence (8.6%) of high-risk HPV among females aged 18–59 years.[51] There is also evidence of the low utilization of either mammography (10%) or a Pap smear test (12%), as well as the low awareness of HPV and the HPV vaccine (21% and 18%, respectively) among Georgian women of reproductive age that has been attributed to their lack of knowledge or reluctance to access preventive services or providers' lack of expertise or the absence of perceived job responsibility to offer such services.[18,52] Our results, therefore, could guide strategies for further strengthening the National Reproductive Tract Cancers Prevention and Early Detection Program, initiated in 2006 and expanded nationwide in 2011,[53] to curtail cancer epidemic and reduce mortality in the Georgian female population, who might also benefit from fertility preservation during their child-bearing years.[54]

The observed high death toll of CVD, the second major NCD-related cause, with the most common cerebrovascular diseases and IHD, mirrors global evidence on increasing importance of these conditions in rankings of the top 10 causes of female premature death (years of life lost), with much faster advancement in LMICs.[3,4,6,39] This also makes CVD the second leading cause of death in women of reproductive age worldwide.[6] Similarly, across the WHO European Region, except for Western Europe, both IHD and stroke are among the top three major causes of death in this age group, though ranking in the reverse order, contrary to our findings.[41] Compared to Nordic countries, the burden for women is more than double toward the east, including in Central Asia and Russia, and most likely reflects the East–West gap in CVD mortality driven by social and political forces, mass psychological stress, and changes in risk factor profiles in post-communist republics since the breakup of the Soviet Union.[6,13,40,41] Recent plateauing of IHD mortality

trends in women aged under 45 years in some European countries, including Russia, has been linked to increasing prevalence of risk factors, such as diabetes and obesity, and plateaus in the prevalence of hypertension in the younger age groups.[55,56] While diabetes, metabolic syndrome, and tobacco use are the well-established predictors of CVD in young women than in their older counterparts, recent epidemiologic studies suggested nontraditional risk factors, such as preterm delivery, hypertensive pregnancy disorders (including preeclampsia), gestational diabetes, autoimmune diseases, breast cancer treatment, and depression to be the important contributors as well, with preeclampsia being associated with increased risk of both IHD and stroke into later life.[57–59] At the same time, compared to men, women, particularly the young (<50 years), are more likely to experience poorer outcomes of a CVD event in part because of underestimation of their risk, delay in diagnosis, or less aggressive treatment on the part of clinicians who are possibly misled by a somewhat different presentation of disease and known protective physiologic effects of estrogen against CVD.[2,41,57,58] Given also exceedingly common undetermined or cryptogenic causes of early-onset stroke mostly at younger ages (<30 years), the overall burden of CVD in young adult women is prone to being underestimated in the face of alarming levels of associated mortality.[59] The implied need for more close follow-up and comprehensive management of the underlying diseases in the high-risk groups of young women gains increasing importance in view of the current concept of "obstetric transition", describing a global shift of direct obstetric causes of maternal mortality toward indirect causes mainly owing to chronic diseases (primarily CVD) with aging of maternal population.[60] Our findings, documenting high mortality from both NCDs and maternal causes, may, therefore, serve as the indirect proof of the critical need for accelerating remedial actions on preventable maternal deaths with the greater focus on interactions between reproductive and noncommunicable conditions.[1,2]

Additional findings with important policy and program implications include the emergence of liver cirrhosis among the 10 leading causes of death in women of reproductive age, with subsequent TB as the most common communicable cause. Our findings are comparable with the global data indicating both diseases to be the leading causes of death (seventh and fifth, respectively) in this age group of women.[6] Likewise, liver cirrhosis ranks among the top five causes of death in young women in all parts of the WHO region, whereas TB ranks fifth in Central Asia.[41] The observed high mortality from liver cirrhosis in our study population, particularly pronounced in the oldest age group, likely reflects Georgia's one of the world's highest prevalence rates (6.7%) of hepatitis C virus (HCV) infection owing to iatrogenic transmission and injection drug use, as opposed to other former Soviet Republics in Eastern Europe, where the increasing burden of liver cirrhosis has been predominantly driven by heavy alcohol consumption.[6,61–63] Our findings are also consistent with the recent research in the general female population from nine developing countries, identifying Georgia as the third highest female HCV prevalence (1.3%) country after Mongolia and Pakistan and suggesting interventions/hospitalizations due to childbirth, but not sexual transmission, to be a possible route of HCV transmission in the study sites.[64] The same study also indicated that a steady increase in female HCV prevalence with age (prevalence ratio for ≥45 versus <35 years=2.84, 95% CI=2.18 to 3.71) is likely to be attributable to the combination of accumulating risk of exposure and a high probability of infection becoming chronic, and confirmed a correlation between age-specific HCV prevalence and related liver cancer incidence in those aged ≥45 years.[64] Furthermore, previous study in Georgia found the high prevalence of HCV coinfection (21%) among TB patients (median age 37 years) most likely owing to drug-induced hepatotoxicity.[65] This has been shown to be associated with increased risk of liver cirrhosis, and conversely, HCV and cirrhosis with increased risk of developing active TB disease.[66,67] Georgia, like other former Soviet Republics, has been among the worst-affected countries by TB since the collapse of the Soviet Union and currently ranks among the world's 27 high multidrug-resistant-TB (MDR-TB) countries that hinder effective TB control.[68–70] Moreover, while previous treatment has been documented as a major risk factor for MDR-TB in the European Region, with Eastern Europe and Central Asia showing the world's highest rates, studies in Georgia identified female gender as another independent predictor of MDR-TB, imitating the findings from two studies conducted in Russia and Estonia.[68,69] Besides this, a substantial proportion of reproductive-aged women in the GRHS10 reported TB exposure through interactions with either infected family members (9%) or the other sources (12%).[18] Hence, our results highlight the importance of improving surveillance and treatment programs for liver cirrhosis and TB, preferably in an integrated manner, to more effectively and efficiently reduce the associated heavy burden in women of reproductive age, addressing at the same time a vertical HCV transmission risk during pregnancy[71] and increased risk of perinatal deaths (sixfold) or premature birth and low birthweight (twofold) related to TB.[72]

Our study findings further emphasize the crucial need in the country for prevention of fatal injuries, remaining overall the second leading cause of death and the principal cause in those aged under 25 years. Of special concern are road injuries, the second major cause, and violence, particularly suicide, the seventh leading cause, collectively accounting for over one-third (35%) of deaths in those aged 15–29 years, thus the prime child-bearing age group in Georgia.[18] Our findings are consistent with the WHO data for Georgia and the European Region,[73,74] as are with global patterns of injury mortality, showing road injuries to be the principal cause of death in the 15–29-year age group, followed by suicide, yet with males most affected.[75] Contrary to the global ranking of tenth place, road injuries in Europe and Central Asia rank sixth as a cause of premature death and disability, while ranking fourth among women of reproductive age in Eastern Europe.[40,41] The rising, yet neglected, burden of road traffic deaths in LMICs, contributing to >90% of fatalities worldwide, has been associated with increased urbanization and motorization, particularly in emerging economies, coupled with a lack of sufficiently improved road safety strategies.[75] In recognition of this health and development problem, Georgia has recently addressed the well-established risk factors of road traffic accidents by setting and enforcing traffic laws governing speed limits, drunk driving, distracting driving, and mandatory use of seat belts and helmets, in addition to improving the road infrastructure.[73,75] However, our study results imply that clearly defined road safety policy, strict implementation of proven interventions, and reliable information systems are still required to reduce the burden of road traffic fatalities in the country.[73] A special attention has to be drawn to violence as well, particularly in those at younger ages. Adolescents are exceptionally susceptible to violence death, predominantly suicide, known to be largely triggered by depression, eating disorder, other mental disorders, loneliness and hopelessness, relationship breakdown or interpersonal problem, or adverse childhood experience, such as physical and sexual abuse or victimization by bullying.[76,77] There are also increasing concerns about the role of the social media in suicide communications among the young.[76] Importantly, depression is among the top two leading causes of disability in women aged 15–49 years in all subregions of the WHO European Region.[41] Overall, as most of the global suicide deaths are disproportionately concentrated in LMICs (78%),[76] some of the world's highest suicide rates documented in former Soviet Republics have been correlated with the post-Soviet transitional period and a wide range of socioeconomic, cultural, and religious factors, with unemployment and income inequality shown to be stronger predictors of female suicide.[6,33,34,78] Studies from Georgia highlighted deep-rooted patriarchal attitudes and gender stereotypes as the important drivers of intimate partner violence (IPV) among ever married women of reproductive age (4%) who were 2–4 times more likely to justify IPV in at least one scenario, compared with those who had no such experience.[18,79] This was particularly evident among poor, rural, less educated, unemployed, and younger women, as well as those with a history of child abuse or parental IPV.[79] This in turn is known to be associated with increased risk of IPV[80] and suicidality.[76,77,81] Furthermore, the cross-sectional study on conflict-affected internally displaced persons aged >18 years in Georgia found that, compared to men, women were more likely to have posttraumatic stress disorder (PTSD), depression, and anxiety due to trauma exposure, forced displacement, daily stressors, and impoverishment.[82] This warrants further research, given a well-recognized relationship between PTSD and suicidal behavior mediated by comorbid depression irrespective of the type of trauma experienced.[81] Taken together, our study findings underline the urgent need for multisectoral prevention and control interventions addressing violence, both self-inflicted and interpersonal, with a special focus on the availability of key data, law enforcement, and service accessibility for victims to ensure effective response.[73]

Limitations

Our study had a number of limitations. First, underlying causes of death could not be determined for 35 eligible women because of a failure to reach their families and complete VAs. However, there is little reason to expect such a small percentage of missing causes (only 3.8%) to have significantly biased our findings. In addition, 39 deaths (4.4%), lacking clear symptom patterns, were assigned to ill-defined codes in VA data, yet accepted within a reasonable range, given the retrospective nature of the data collection.[11] Second, the relatively long recall period of 2 years could have influenced the respondents' ability to correctly recall events. On the other hand, previous research, indicating no major differences in the impact of the longer and shorter recall intervals, suggested 3 months to 2 years to be the most optimal delay range after a death.[9–11] Other potential biases in VA-based cause-of-death ascertainment could be related to the well-recognized limitations of this method likely linked to instrument design, selection of respondents, variability in interviewers' skills, and physicians' approaches to death certification and coding.[9,83,84] Finally, although acknowledging these limitations, our study used VA diagnoses as a reference

standard to assess the diagnostic accuracy of the CRVS system. However, our decision, driven by a very low percentage of hospital deaths (28%) in the study sample, was supported by other studies, which used the same approach.[36,37] Besides this, despite all of its shortcomings, earlier validation studies highlighted a good level of performance of physician-certified VA for some important specific causes of death in adults, particularly for breast cancer, maternal causes, road injuries, homicide, and, to some extent, suicide and stroke.[84]

Conclusion

Understanding the full dimension of women's health risks during the reproductive years based on reliable data on causal patterns of mortality is of critical importance to inform evidence-based health policy and develop robust strategies addressing avoidable premature female mortality. Our study underscores that VA is a feasible tool for filling in existing gaps in national cause-of-death data, thus yielding essential information on key age- and sex-specific health priorities. This study identified NCDs, with cancers dominant, to be the major health threats for Georgian women of reproductive age. While our findings may contribute to the limited global evidence on the special challenges adolescent and young adult women face in the less developed world, they could also serve as a baseline knowledge for tracking progress toward broader national development goals. Further detailed research is needed to advance our knowledge of emerging health problems and their determinants in this population for effective application of health promotion and risk reduction interventions to be focused on NCDs and reproductive health needs with an integrated approach.

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Disclosure

The authors report no conflicts of interest in this work.

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ORIGINAL RESEARCH

Maternal Mortality in Georgia: Incidence, Causes and Level of Underreporting: A National Reproductive Age Mortality Study 2014

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Introduction: Accurate data on maternal mortality are essential for assessing progress towards Sustainable Development Goals (SDG).The aim of the study was to determine the incidence and causes of maternal deaths in Georgia, then explore the potential for improvement of quality of maternal health care. The study's secondary aims were to identify the level of underreporting of maternal deaths in Georgian vital statistics over 1 year (2012) and to compare these results with previous data from 2006. The study findings allow to support the country in developing evidence-based policies and tracking progress towards meeting SDG targets.

Methods: A national Reproductive Age Mortality Survey (RAMOS) was conducted in Georgia in 2014–15. Multiple data sources were used to identify deaths of women aged 15–49 years between January and December 2012. All deaths in women of reproductive age were investigated through verbal autopsy (VA) diagnoses. Deaths in women during pregnancy or one-year postpartum were further investigated by conducting interviews and medical record reviews at the last medical facility which provided health care for the woman during her fatal condition. A specialist panel reviewed these cases and assigned underlining causes of deaths.

Results: We found that 98% of deaths among women of reproductive age were registered by Georgia's civil registration and vital statistics system (CRVS). A total of 918 deaths met the study inclusion criteria. Thirty-six (4.1%) women died during pregnancy or within one-year postpartum. Among these 36 deaths, 23 (63.8%) were maternal deaths, 15 early (either during pregnancy or 42 days postpartum) and eight late (43–365 days postpartum) deaths (65.2% vs 34.8%). The remaining 13 of 36 deaths were coincidental deaths. Fourteen maternal deaths were reported by official statistics and nine deaths were not included in these statistics. Thus, the underreporting rate was 39%. Direct obstetric causes accounted for 73.9% (n=17) of maternal deaths, whereas 26.1% (n=6) were indirect. The leading causes of direct maternal deaths were infection (21.7%), hemorrhage (17.4%), pulmonary embolism (13.0%), and pregnancy-induced hypertension (8.7%). The RAMOS study calculated a maternal mortality ratio (early maternal deaths) of 26.3 per 100,000 live births compared with the official figure of 22.8 per 100,000 live births.

Discussions: Registration of early maternal deaths significantly improved since last survey in 2008, while indirect and late maternal deaths continue to be unrecognized, as reflected in official Georgian statistics. The difference between RAMOS study findings and officially reported maternal mortality rates is minimal, showing improvements in detection of maternal deaths by the national maternal mortality surveillance system. The greatest number of direct obstetric deaths occur in the first week postpartum, which likely reflects deficiencies in quality of care.

Keywords: maternal mortality, maternal death, incidence, causes, underreporting of maternal deaths, verbal autopsy, reproductive age mortality study

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Introduction

Maternal mortality data and tracking the causes of maternal death are two principal indicators of overall maternal health and markers of the health system performance.[1,2]

Since adoption of the Millennium Development Goals (MDG), significant progress has been made in reducing maternal deaths. Globally, maternal mortality ratios have been almost halved between 1990 and 2015.[3] Unfortunately, achievement of the MDG target to reduce the rate of maternal mortality by three-quarters by 2015 fell short globally, including in Georgia. To reassert the importance of this unfinished agenda of maternal mortality reduction, Sustainable Development Goals (SDGs) adopted by the United Nations (UN) set a target to reduce the global maternal mortality ratio (MMR) to less than 70 per 100 000 live births. The national target for maternal mortality in the SDG framework is that all countries should reduce their MMR by at least two-thirds from the 2010 baseline and achieve equity in maternal mortality levels for vulnerable populations at the subnational level.[4,5]

Georgia, situated in the South Caucasus, is a lower-middle-income country with a population of 3.7 million.[6] Since its independence in 1991, Georgia has gone through considerable political, economic and social turmoil. Despite recent economic growth, poverty remains the key economic and social issue for the country.[7]

Routine data on maternal mortality in Georgia comes from the national vital registration statistics (CRVS). The maternal mortality ratio in Georgia fell from 49/100 000 in 2000 to 21/100 000 live births in 2010.[8] An increased share of poorly defined causes of death among all reported mortality in Georgia from 2007, reaching 55% in 2010, was observed.[9] Reliance on hand delivery system for registration of deaths, poor completion of vital documents, inadequate quality control measures, lack of appreciation on the public health importance of proper death certification by the medical professionals were among key problems in the mortality measurement. The high proportion of ill-defined causes and significant difference between official statistics and international surveys has created uncertainty for policymakers about the actual level and trends of maternal mortality in the country.

Periodic population-based studies, such as RAMOS or census-based mortality studies are valid alternatives to relying solely on routine data sources to measure maternal mortality. These studies also provide a source of more detailed information about the actual circumstances of maternal deaths.[10] The first Reproductive Age Mortality Study in Georgia was conducted in 2008 (RAMOS08). It attempted to determine the true levels of maternal mortality in Georgia in 2006.[11] The study showed that national statistics significantly underestimated maternal mortality. Also, both underreporting and misclassification of causes of deaths were major issues in maternal mortality measurement. Only 84% of deaths in women of reproductive age (WRA) were registered, and 65% of all maternal deaths went unreported. In terms of the main causes of maternal deaths, hemorrhage, pregnancy-induced hypertension and sepsis were the leading causes identified by RAMOS08.

From 2010 and onward, Georgia implemented several important initiatives to improve maternal deaths registration and surveillance. Georgia civil registration reform introduced regulations and interventions (eg, a monetary penalty for responsible bodies for failing to report death events, electronic medical death certificates [as opposed to paper] and a pregnancy checkbox on the death certificate) to improve maternal death registration. The Georgian Statistics Office began to match maternal death certificates to birth and fetal death certificates. The National Centers for Diseases Control and Public Health (NCDC & PH) introduced active surveillance of maternal mortality by incorporating WRA deaths into integrated electronic disease surveillance system (IEDSS) and implementing the verbal autopsy methodology to review all pregnancy-related deaths. On the medical side, specific protocols, guidelines and training programs for the management of common causes of maternal deaths were developed and implemented. Despite these improvements, accurate reporting on the cause of death reporting remains a challenge.

A second RAMOS was conducted in Georgia in 2014 (RAMOS14), using retrospective 2012 data. In this study, we assessed the magnitude of maternal mortality and its causes, enabling comparison to the similar survey conducted in 2008, based on 2006 data. We also investigated progress and accuracy of the official statistics in reporting maternal deaths. Findings from the study were used as the basis for the development of an action plan and policies to further reduce preventable maternal deaths, improve maternal death reporting and enhance quality of care.

Materials and Methods

Definition of Terms

We used the definition of maternal death and underlying causes of death classification from the World Health Organization (WHO) Application International Statistical

Classification of Diseases and Related Health Problems, 10th Revision (ICD – 10) to deaths during pregnancy, childbirth and puerperium: ICD MM.[12] WHO defines maternal death as

> the death of a woman while pregnant or within 42 days of termination of pregnancy (0-42 days postpartum), irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

We also identified late maternal deaths defined as delayed deaths occurring between 6 weeks (42 days) and 1-year postpartum.

All maternal deaths were included and classified based on their causes as either direct or indirect.

Direct obstetric deaths are the ones resulting from obstetric complications of the pregnant state (ie, pregnancy, labor and the puerperium), from interventions, omissions of- or incorrect treatment, or from a chain of events resulting from any of the above. Indirect obstetric deaths are those resulting from a previous existing disease or one that developed during pregnancy and which was not due to direct obstetric causes but was aggravated by physiologic effects of pregnancy. Coincidental deaths are those deaths that occur during pregnancy, childbirth or the puerperium (42 days) but that are not by definition considered maternal deaths.

The national RAMOS was conducted between March 2014 and January 2015. The target population for the RAMOS study included all women aged 15 to 49 with a permanent residence in Georgia, and who died in 2012. The year 2012 was selected as the most recent year for which full and error-checked databases were available at the initiation of the study.

The research methodology involved investigation of all causes of death to WRA. There were three phases of data collection: death identification, personal interviews with relatives of deceased women using a verbal autopsy (VA) questionnaire and medical record review at the last health facility that provided care for the woman during her fatal condition in pregnancy or 1 year after childbirth. The RAMOS questionnaire contains additional-specific questions about circumstances that may have led to death among women aged 15–49, including cancer and other chronic diseases, intentional or unintentional injuries, and conditions related to or aggravated by pregnancy and its management. The instrument was developed based on questionnaires used in pregnancy mortality studies and surveillance systems conducted by the Centers for Diseases Control (CDC) in the United States and Latin America combined with elements from the WHO verbal autopsy tool.[13] A comprehensive history of use of health-care services prior to death had been added to capture barriers to appropriate and timely care and to facilitate needed improvements in the health system.

Multiple data sources were used to identify potentially eligible WRA cases. These included: 1) the CRVS mortality electronic dataset; 2) routine health statistics and surveillance data from NCDC&PH; 3) hospital and ambulance service registers electronic datasets; 4) regional death registers; and 5) community informants contacted during the field investigation.

Of the 913 eligible deaths to WRA in 2012, verbal autopsies (VA) were completed for 878 (96.2%) deaths (Figure 1).

This second step, VA interviews with family members or caregivers of deceased women, was conducted through household visits. Information about signs and symptoms prior to death was collected through VA questionnaires by trained female interviewers with medical background.

Completed questionnaires were assessed independently by two expert clinicians who were approved by the Ministry of Labor, Health and Social Affairs. They assigned the most probable underlying cause of death based on the international standard death certificate and International Classification of Diseases, 10th revision (ICD-10). Discrepancies in coding were resolved by a third clinician who provided the final coding of each questioned case.

Deaths during pregnancy or one-year postpartum were further investigated by a review of hospital medical records. A multidisciplinary panel of medical experts experienced in classification of pregnancy-related causes of death categorized pregnancy-related deaths as maternal deaths, “direct” or “indirect”, or as “co-incidental”. The panel also defined one main cause of death and assessed contributing circumstances and commented on preventability.

Data analysis was performed using SPSS version 21.0. Data were analyzed using simple descriptive methods with frequencies and cross-tabulations. Patterns of misclassification between CRVS, VA diagnoses and multidisciplinary panel of medical experts were further analyzed by cross-tabulating these data.

Ethical Approval

The study protocol was approved by the Georgian Institutional Review Boards of NCDC & PH (IRB 2017-035 and 2019-013) and the Regional Committees for Medical and Health Research Ethics South East Norway (2015/1352). Written informed consent was obtained from

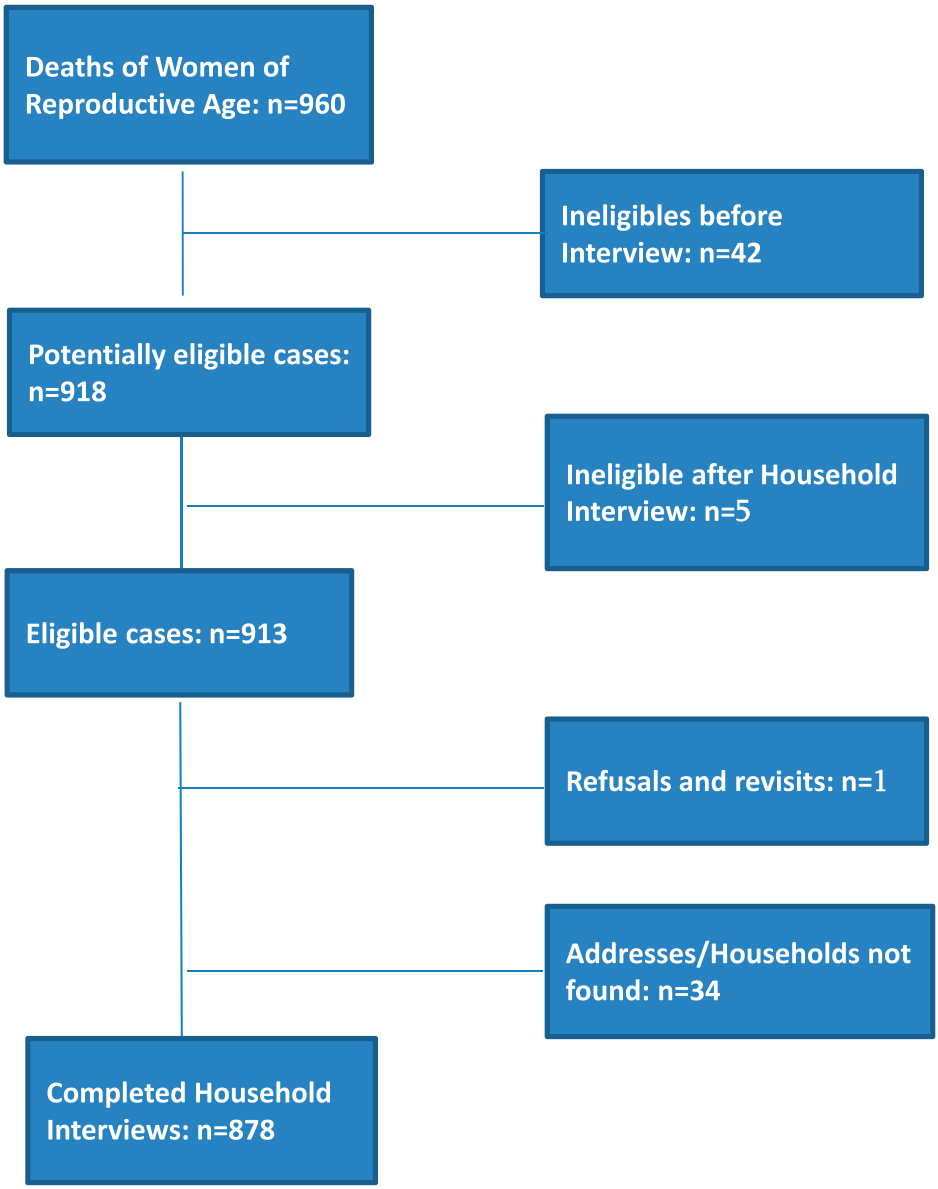

Figure 1 Case identification (2014–15) of study eligible maternal deaths Reproductive Age Mortality Study: Georgia, 2014.

all respondents (family members or caretakers of the deceased women) prior to interviews.

Results

Characteristics of the Maternal Death Study Population

In 2012, 57,031 live births were registered in Georgia. A total of 36 pregnancy-related deaths was identified. Among these, 23 (63.9%) deaths were classified as maternal, directly or indirectly caused by pregnancy and 13 (36.1%) as deaths from co-incidental causes. Of the 23 maternal deaths, 15 (65.2%) were early and eight (34.8%) were late.

Of the 23 maternal deaths, about half of the women were 20–29 years of age at the time of death; 39% were 30–39 years; and 13% were 40 years or older. We found the highest age-specific maternal mortality ratio in the older age groups (35–39 and 40–44), and the lowest in age group[25–29] (Table 1).

Time of Death

A total of 23.1% of the women died during pregnancy, 30.4% of the maternal deaths occurred during the first postpartum week, and 13.0% within 8–42 days postpartum. The remaining 34.8% were late maternal deaths, occurring 43–365 days postpartum.

Table 1 Distribution of Live Birth by Age Groups and Age-Specific MMRs in Georgia in 2012

Age Groups	Distribution of Birth by Maternal Age	Age-Specific MMRs per 100 000 Live Births	
	N (%)	N	Ratio
15–19	5662 (9.9)	0	0.0
20–24	19,571 (34.4)	8	40.9
25–29	16,833 (29.6)	3	17.8
30–34	9734 (17.1)	5	51.4
35–39	4131 (7.2)	4	96.8
40–44	980 (1.7)	3	306.1
45–49	91 (0.2)	0	0.0
Total	57,002 (100)	23	

Pregnancy Outcomes

Among the 23 maternal deaths, 52.2% (n=12) followed delivery of a live birth and 8.7% (n=2) occurred after a stillbirth, while 13% (n=3) were still pregnant at the time of death. 17.4% women (n=4) died after early fetal loss (three miscarriages, one ectopic pregnancy) and two after induced abortions (Table 2).

Causes of Deaths

Direct obstetric deaths constituted 73.9% (n=17) of all maternal deaths. The four leading causes were sepsis, hemorrhage, pulmonary embolism and preeclampsia/eclampsia (Table 3).

Other direct causes of deaths were sudden death (n=1), unanticipated complication of anesthesia during delivery (n=1) and complication following intrauterine fetal death (IUFD) at term (n=1).

Among the indirect maternal death causes, cancer was the most common (n=3), whereas tuberculosis, bacterial meningitis and postpartum suicide resulted in one death each (Table 3).

The 13 (36.1%) coincidental deaths (i.e., causes unrelated to pregnancy) were transport accidents (n=2) and other accidents (n=4), cancer, representing brain and retroperitoneal tumors (n=6), and liver cirrhosis (n=1).

Mode of Delivery

Of the 14 deceased women whose pregnancies resulted in a live birth or stillbirth, 57.1% (n=8) delivered by Cesarean section (CS) and 42.9% (n=6) had assisted vaginal deliveries. Four CSs were performed due to previous CS, one for pre-existing medical condition, one for preeclampsia, one due to obstructed labor and one without any medical indication. Of all CSs, 37.5% (n=3) were followed by postoperative infections, 25% (n=2) by postpartum embolism, and one was related to complication of anesthesia.

Maternal Deaths Underreporting

Fourteen (60.9%) of the 23 maternal deaths documented in this study were officially recognized by the Georgian vital registration system as maternal. Only one of the eight late maternal deaths was reported in official statistics. Additionally, two early maternal deaths went unrecognized by the official statistics (Table 4).

Incidence and Reporting

We found an overall MMR (early and late maternal deaths) for 2012 of 40.3 per 100 000 live births, which is a 38.5% reduction compared to the MMR of 65.6 per 100 000 live births in 2006.[11] Early maternal mortality declined by 40.8%, from 44.4 per 100 000 live births in 2006 to 26.3 per 100 000 in 2012 (Figure 2).

Discussion

This paper presents the nationwide maternal mortality data from Georgia in 2012 (named RAMOS14). We found both a decreased incidence and an improvement in reporting maternal deaths as compared with 2006 (named RAMOS08) findings. This trend reflects similar trends in the WHO European Region. Over the past decade, many

Table 2 Pregnancy Outcome in Pregnancy-Related Deaths in Georgia, 2012

RAMOS Classification	Total	Outcome of Pregnancy				
		Induced Abortion	Other Fetal Loss*	Stillbirth	Pregnant	Livebirth
Maternal deaths n (%)	23	2 (8.7)	4 (17.4)	2 (8.7)	3 (13.0)	12 (52.2)
Direct obstetric death	17	1	3	1	3	9
Indirect obstetric death	6	1	1	1	0	3
Coincidental deaths	13	2	1	0	3	7
All Pregnancy-related deaths	36	4	5	2	6	19

Note: *Ectopic pregnancy or miscarriage.

Table 3 Causes of Maternal Deaths in Georgia in 2012 by the Time of Death

	All Maternal Deaths	Early Maternal Deaths (0–42 Days pp)	Late Maternal Deaths (43–365 Days pp)
	N=23 (%)	N=15 (%)	N=8 (%)
Direct Causes			
Sepsis	6 (26.1)	5 (33.3)	1 (12.5)
Hemorrhage	3 (13.0)	3 (20.0)	0 (0.0)
Embolism	3 (13.0)	1 (6.7)	2 (25.2)
PIH	2 (8.7)	2 (13.3)	0 (0.0)
Other direct	3 (13.0)	3 (20.0)	0 (0.0)
Indirect causes	6 (26.1)	1 (6.7)	5 (62.5)
Total	**23 (100.0)**	**15 (100.0)**	**8 (100.0)**

countries in the WHO European Region have made substantial progress in reducing maternal mortality. The average-estimated maternal mortality ratio for the region decreased by more than half from an average 33 maternal deaths per 100 000 live births in 2000 to 16 in 2015.[9] Despite a decreasing trend, the estimated number of maternal deaths in 2015, in Georgia is much higher than the WHO European region estimate. The estimate-36 maternal deaths per 100,000 live births is concerning.[9] Georgia has the highest maternal death rate among the Black Sea and neighboring countries.[9,14] On the other hand, it is important to note that countries with accurate maternal mortality surveillance systems and continuous audits report higher MMR than countries without these implemented initiatives. Thus, it is plausible that the very low mortality ratios in some countries may be due to systemic underreporting of maternal deaths, lack of national registers, or problems with completeness of ascertainment or suboptimal procedures for coding rather than higher quality services.

In our study, the age group 25–29 had the lowest MMR and it increased with increasing age. The age-group 40–44 had an almost a 20-fold increased risk of MMR compared to the 25–29 age group. Advancing age is associated with increased adverse outcomes in pregnant women. According to most studies, a maternal age of 35 years is the threshold for a significant increased maternal morbidity and mortality and our findings are in accordance to these studies.[15]

More women with pregnancy-related deaths lived in urban areas than in rural areas 60.9% vs 39.1%. The clear majority were married at the time of death. Women with medium and low socioeconomic status were at higher risk for maternal death. One-third of maternal deaths occurred among women living at subsistence or below subsistence levels. The high probability of not receiving care among women living in households with the lowest wealth quintile and having poor health outcomes are well documented and our findings are in line with these studies.[16,17]

All 36 pregnancy-related deaths included in our study were officially reported in the vital registration system, whereas only 85.7% were reported in 2006.[11] This represents a significant improvement in death registration coverage in Georgia, reported by WHO as well (98%).[15] The improvement is most likely due to major reforms

Table 4 Death Reported in the RAMOS14 Study and the Official Maternal Mortality Statistics Deaths to Currently or Recently Pregnant Women Aged 15–49

RAMOS Classification	Pregnancy-Related Deaths			Maternal Deaths		
	RAMOS	Officially Reported		RAMOS	Officially Reported	
	N	N	%	N	N	%
Total	36	36	(100.0%)	23	14	(60.9%)
Early deaths (0–42 days pp)	20	13	(65.0%)	15	13	(86.7%)
Direct obstetric deaths	14	12	(85.7%)	14	12	(85.7%)
Indirect obstetric deaths	1	1	(100.0%)	1	1	(100.0%)
Coincidental deaths	5	0*	†	†	†	†
Late deaths (43–365 days pp)	16	13	(81.3%)	8	1	(12.5%)
Direct obstetric deaths	3	1‡	(33.3%)	3	1‡	(33.3%)
Indirect obstetric deaths	5	0	†	5	0	†
Coincidental deaths	8	12*	(150.0%)	†	†	†
Other§	0	10	†	†	†	†

Notes: *Virtually all death certificates of WRA lacked the pregnancy status specified (empty pregnancy check-box); late coincidental deaths identified by data matching include six late maternal deaths classified by RAMOS14. †Not applicable. ‡Reclassified as indirect in RAMOS14. § Pregnancy-related deaths to women aged 15–49 identified by RAMOS14 including 3 maternal deaths.

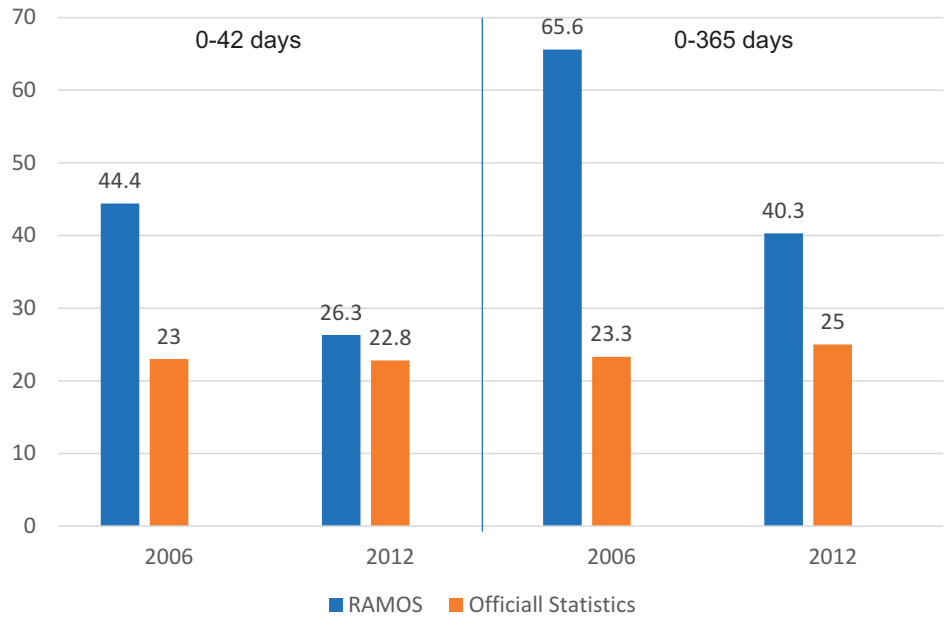

Figure 2 Maternal Mortality Ratios (MMR) per 100,000 Live Births RAMOS 2008 and RAMOS 2014 and Official Reports of Maternal Deaths in 2012 and 2006.

implemented in the CRVS described earlier and implemented because of results of the first RAMOS.

Georgia's official statistics reported a MMR of 22.8 compared to findings of 26.3 in RAMOS14. This is a relatively small gap between the official statistic and RAMOS14 (Figure 2). The trend of minimal difference between official statistic and estimations via special studies continued to be present in 2015, when official statistics reported 30 maternal deaths per 100 000 live births compared to the estimated maternal mortality of 36 female deaths per 100,000 live births.[3]

Similarly, to other European countries, reporting direct maternal causes in Georgia is comparatively more accurate than reporting on indirect causes or late maternal deaths. Our study shows that 39.1% of maternal deaths went unreported. Similar underreporting of maternal deaths was found in Austria and the Netherlands where overall underreporting was 38% and 33%, respectively.[18,19] However, we documented remarkable improvement since 2006, when 64.5% of maternal deaths went unreported. These significant improvements in Georgia in the systems for registering the deaths of women of reproductive age and maternal death identification were made because the country implemented statewide reforms, as described in the introduction. The results of our study indicate importance of periodic assessments of the quality of routine mortality statistics for reporting maternal deaths and related public health actions. Our study also highlights that comparison between countries should not be restricted to maternal rates published by the national offices responsible for death statistics, but also verified by special studies.

Causes of Maternal Deaths

The finding that 79.3% of maternal deaths had direct obstetric causes is in line with data from 2006 (RAMOS08). Sepsis and hemorrhage were the leading obstetric causes of death, followed by embolism and preeclampsia, which points to issues of quality of hospital care. In contrast, major contributors to maternal deaths in high-income countries in Europe are preeclampsia, cardiac disease and thromboembolism.[20]

Although nationally in Georgia, the rate of hospital deliveries is 99%, quality of care improvements must still be made to reduce maternal deaths. Efforts to improve the quality of care at the hospital level were accelerated beginning in 2010. These efforts included: nationwide training of multidisciplinary teams of providers dealing with obstetric emergencies; development of evidence-based clinical practice guidelines and enforcement of their implementation by the government health authorities; monitoring of hospital clinical quality indicators; and near-miss maternal case reviews. Despite these efforts, our findings highlight an ongoing need to further improve the quality of care at the point-of-care detection as well as gaps in appropriate management of major pregnancy-related events. Most women (90%) had at least four antenatal visits. Indirect causes of maternal deaths in our study suggest weaknesses at the primary care level. In

addition, preconception care, which plays a critical role in timely detection of diseases such as cancer and tuberculosis, is lacking.

Although recommended by the WHO model, postpartum care after discharge from the hospital in Georgia is focused on health and development of the newborn, while woman typically receive no or little follow-up. Our study findings related to timing of death, highlights a need to strengthen postpartum follow up and to reinforce the role of family doctors in postpartum care, especially improvement of early identification of complications and timely referral for specialized care.

It is noteworthy that our research (RAMOS14) revealed only one direct maternal death related to unsafe induced abortion performed by the woman herself after 12 weeks of gestation. This is an improvement compared to the three direct maternal deaths caused by unsafe medical abortions found by RAMOS08. Improved safe abortion practices and post-abortion care may be a factor in the relatively low death rate from induced abortion. On the other hand, the study showed an increase in maternal deaths associated with miscarriages compared to the previous study, where no miscarriage-associated maternal deaths were reported.

Despite an increase in contraceptives use by married women or in union from 41% in 1999 to 53% in 2010, 65% of married women still have a potential demand for contraception.[21] Improved access to contraceptive commodities and safe and effective use will likely help reduce the risk of maternal death posed by unintended pregnancies and adverse pregnancy outcomes in women with poor health.[22]

Caesarian sections (CS) were performed in 57% of the women who died. The increased CS rate from 20.7% (2006) to 36.7% (2012) is worrying, but also in line with international trends.[23,24] CS performed for maternal request, medicolegal reasons, provider and patient-driven medicalization of birth are possible explanations of the rise in Georgia, repeatedly reported in studies from many countries.[8,25,26] While RAMOS08 found that the majority (95%) of CSs were emergency and life-saving, RAMOS14 revealed that only a quarter of CSs were emergency interventions performed on the same day the women initially presented for care. In our study maternal mortality was 14.0 per 100,000 live births for CS and 12.3 per 100,000 for vaginal births. This finding is in line with other studies from developed countries where the chance of dying from a CS is rare, but it's a little higher than a vaginal delivery.[27]

The potential benefits of CS in saving maternal and infant lives in emergency situations have been accepted globally in medical practice, but there is no evidence showing the benefits of CS for women or infants when surgery is not medically indicated. On the contrary, CS carries an increased risk of maternal mortality and severe acute morbidity and increases complication rates in subsequent pregnancies.[28] CS complications, such as sepsis and thromboembolism, were two of three leading causes of maternal deaths in our study.

No maternal deaths identified in the study had been followed by an autopsy. The practice of postmortem examinations needs to be improved to help physicians determine the primary and underlying causes of death. The low uptake of postmortem examination has not been widely studied in Georgia. Likely factors found in other studies encompass not only cultural, but professional and organizational.[29]

Conclusions

In our study, we found a significant improvement in death registration coverage, decreased incidence and an improvement in reporting maternal deaths as compared with previous, RAMOS08 findings. The improvement in reporting was particularly prominent for early maternal deaths. The causes of deaths were mainly direct with sepsis as the number one diagnose.

Our study supports the hypothesis that a well-organized vital registration system is important for policy-making and to drive decisions on quality of care in maternal health. However, a vital registration system alone cannot address issues of misclassification of maternal deaths. Therefore, active surveillance, routine nationwide data linkage and audits are essential.

The major strides made over the last decade in Georgia to improve maternal and neonatal care have had a real impact, when measured in the reduction of maternal deaths. While still above the European Union (EU) average, the maternal mortality rate in Georgia has fallen. Despite this progress, we suggest that maternal health and survival remain high on the public agenda and that effective reforms continue to promote the goal of ending preventable maternal deaths in Georgia.

Ethics and Consent Statement

Georgian Institutional Review Boards of NCDC & PH (IRB 2017-035 and 2019-013) and the Regional Committees for Medical and Health Research Ethics South East Norway (2015/1352).

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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III

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ORIGINAL RESEARCH

Audit of Early and Late Maternal Deaths in Georgia: Potential for Improving Substandard Obstetric Care

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Introduction: Quality of care is an important factor in reducing preventable maternal deaths, yet it is a significant challenge in many countries. Substandard and poor quality of care is the leading factor in two-thirds of maternal deaths in European countries. Our study investigated the deaths of all women of reproductive age in 2012 in Georgia. The aim was to define the underlying causes of maternal deaths and to identify the factors in women's care which contributed to the fatal outcomes.

Methods: A national Reproductive Age Mortality Survey was conducted in Georgia in 2014–15. Data from multiple sources was triangulated to identify all deaths of women of reproductive age. This was followed by verbal autopsy diagnoses. Each case of early and late maternal death was investigated through interviews and medical record reviews at the last medical facility providing care for the deceased woman. A specialist panel reviewed and assigned underlying causes of death, assessed the management of each woman's condition, and identified elements of suboptimal care.

Results: We identified a total of 23 maternal deaths, including 15 (65%) early and eight (35%) late deaths. The maternal mortality ratio was 26.3 per 100 000 live births. The four leading causes of early maternal deaths were: sepsis, hemorrhage, embolism, and pregnancy-induced hypertension. Embolism and sepsis were the direct causes of the eight late maternal deaths. Cancer, tuberculosis, and postpartum suicide constituted the indirect causes of death. Improvements in care which would have made a difference to the outcomes were identified in 87% of early maternal deaths and 67% of late maternal deaths due to direct obstetric causes.

Discussion: Delayed recognition and inappropriate management of maternal complications were common across almost all cases studied. The findings from Georgia highlight the conclusion that most maternal deaths were preventable and that improvement in obstetric care is urgently required.

Keywords: maternal mortality, late maternal death, cause of death, quality of care, maternal death preventability

Introduction

Although maternal mortality has declined globally by 38% over the past two decades,[1] the dominant and most common direct causes of maternal death remain postpartum hemorrhage, hypertensive disorders and maternal sepsis.[2] Still, indirect causes have been playing an increasing role in maternal mortality, globally.[3,4] These causes include cardiovascular disease, cancer, mental health disorders, infectious diseases and non-genital sepsis.[3,4]

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While the maternal mortality ratio in Europe is relatively low in comparison with other regions of the world, there is a wide variation in the European Region[1] ([1]As defined by the World Health Organization (WHO), the European Region comprises 53 countries, covering a vast geographical region from the Atlantic to the Pacific oceans.) across countries both in terms of mortality rates and causes of maternal deaths.[1] Importantly, low-income countries have higher levels of maternal deaths from direct obstetric causes in contrast to high-income countries, which are experiencing increasing levels of maternal mortality from indirect causes. This is likely due to the rise in non-communicable diseases (NCDs).

The "three delays" model of maternal care identifies three time points when appropriate interventions can prevent an emergency condition from progressing toward a maternal death. These delays are: (1) in seeking care; (2) in reaching a care facility; and (3) in receiving appropriate care.[5] This model is commonly applied to evaluate factors that may impede women from receiving appropriate medical care. It is estimated that 50–70% of maternal deaths can be prevented simply by assuring that women have access to appropriate and good quality of care.[6,7] Thus, quality of care is an important factor in reducing preventable maternal deaths and a significant challenge in many countries. As shown by confidential enquiries, substandard and poor quality of care is the leading factor in two thirds of maternal deaths in European countries.[8]

The factors influencing quality are complex and interconnected. They include: the availability of infrastructure and supplies; level of training of health care personnel; preparedness of facilities to provide required levels of specialized care when complications arise; adequate and rapid referral systems; and provider-patient relationships.[9,10] Other factors include leadership, governance and accountability for quality. In low- and middle-income countries, maternal mortality reduction is slow due to the limited quality of services provided, combined with poor health system capacity to timely identify and adequately manage pregnancy complications.[11]

Monitoring and clinical auditing of individual maternal deaths, both early and late, can provide insights into different aspects of the quality of services provided and then help define the elements of delay and substandard care which need to be addressed. This process is central for detecting gaps in the health system and recommending policies and improvements to health care decision makers.[12] In addition, many countries focus efforts solely on prevention of early maternal death and too often fail to link late maternal death with missed opportunities in care during pregnancy or after delivery.[13] A late maternal death is defined as death of a woman from direct or indirect causes more than 42 days but less than one year after the end of pregnancy. It has been introduced in the International Classification of Diseases (ICD) 10th Revision because of the current advancements in medical care potentially delaying death after life-threatening complications of pregnancy.[14] Despite its importance, reporting and examining of late maternal deaths has to date been insufficient.

A Reproductive Age Mortality Survey (RAMOS) was conducted in Georgia in 2014 (RAMOS14) in order to ascertain the accuracy of routine statistics and to understand the epidemiology of maternal mortality and its determinants. RAMOS used retrospective data from 2012[15] and assessed the magnitude of maternal mortality and its causes, enabling a comparison to a similar survey conducted in 2008, based on 2006 data. In this study, we assessed each maternal death and identified the main causes of death as well as contributing factors. We also assessed the elements of substandard medical care, including timely identification of risks or complications, adequate and timely referral to the appropriate level obstetric facility, evidence-based management of severe maternal conditions, and timely interventions. Importantly, the study also addresses late maternal deaths, contributing to the knowledge base around these deaths.

Materials and Methods

Study Population

The national RAMOS was conducted between March 2014 and January 2015. The study's target population included all women aged 15 to 49 who were permanent residents in Georgia, and who died in 2012. The year 2012 was selected as the most recent year for which full and error-checked databases were available at the time the study began.

Standard Definitions

In this study we used the World Health Organization (WHO) ICD-Maternal Mortality (ICD-MM) definition of maternal death and underlying causes of death classification and applied these definitions to all reviewed maternal deaths:

> A maternal death is 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.

We also applied the definition of late maternal deaths as "delayed deaths occurring between full six weeks (more than 42 days) and one year postpartum".[16] All maternal deaths were included and classified based on their causes as either direct or indirect. Direct obstetric deaths were standardly defined as

> those resulting from obstetric complications of the pregnancy state (pregnancy, labor and the puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.

Indirect obstetric deaths were those resulting from previous existing disease or disease which developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy.[16]

Data Collection

The triangulation of data from multiple sources was applied to identify potentially eligible women of reproductive age (WRA). Data sources included: 1) the civil registration and vital statistics (CRVS) mortality electronic dataset; 2) routine health statistics and surveillance data from the National Center for Disease Control and Public Health (NCDC&PH) of Georgia; 3) hospital and ambulance service registers and electronic datasets; 4) regional death registers; and 5) community informants contacted during the field investigations. The 2012 number of live births (57,002) reported in the official statistics, CRVS and NCDC &PH data sources, was used to yield maternal deaths per 100,000 live births.

Of the 913 eligible deaths of WRA in 2012 in Georgia, 36 were identified as pregnancy- related deaths (Figure 1). A multidisciplinary panel of medical experts reviewed the medical records of all 36 women who died during pregnancy or within 1 year of termination of their pregnancy, categorized the pregnancy-related deaths as maternal deaths ("direct" or "indirect") or as "co-incidental". The review identified 13 deaths as co-incidental. For the 23 deaths categorized as maternal, a panel of experts conducted additional in-depth reviews of the treatment and care provided to the women and commented on the quality of care and preventability of the death.

The review team considered the existing Georgian national guidelines and clinical care protocols as the reference standard of care for evaluating timely recognition and treatment, appropriate management and referral. Where local guidelines were lacking, we applied guidelines from the Royal College of Obstetricians and Gynecologists (RCOG),[17,18] American College of Obstetricians and Gynecologists (ACOG),[19] and WHO.[20–22] Categorization of the quality of care was made based on the United Kingdom's (UK) scoring system[3] as follows: 1 - good care, 2 - improvements to care which would have made no difference to the outcome, and 3 - improvements to care which would have made a difference to the outcome.

Statistical Analyses

The SPSS version 21.0 (IBM, Armonk, NY, USA) was used to analyze mortality data. We applied univariate, stratified analyses, constructed frequency tables and performed cross tabulation to investigate patterns of maternal mortality in Georgia. The overall MMR was calculated as number of all maternal deaths per 100 000 live births.

Ethical Approval

The study protocol was approved by the Georgian Institutional Review Boards of NCDC & PH (IRB 2017–035 and 2019–013) and the Regional Committees for Medical and Health Research Ethics South East Norway (2015/1352). Written informed consent was obtained from all respondents (family members or caretakers of the deceased women) prior to the interviews.

Results

The study identified a total of 23 maternal deaths during 2012, including 15 (65%) early and eight (35%) late maternal deaths. The overall MMR was 40.3 per 100 000 live births, early MMR was 26.3 per 100 000 live birth. Of the fifteen early maternal deaths, 14 (93%) were direct and one (7%) indirect.

Causes of Maternal Death

The leading causes of maternal deaths were sepsis (n=5), hemorrhage (n=3), pregnancy-induced hypertension (PIH) (n=2) and embolism (n=1) In other direct causes category, sudden death, unanticipated complication of anesthesia during delivery and complication following intrauterine fetal death, were one death in each (Figure 2). Direct causes of the late maternal deaths were: embolism (n=2) and sepsis (n=1). Indirect causes were cancer (n=3), tuberculosis (n=1), and postpartum suicide (n=1). Coincidental

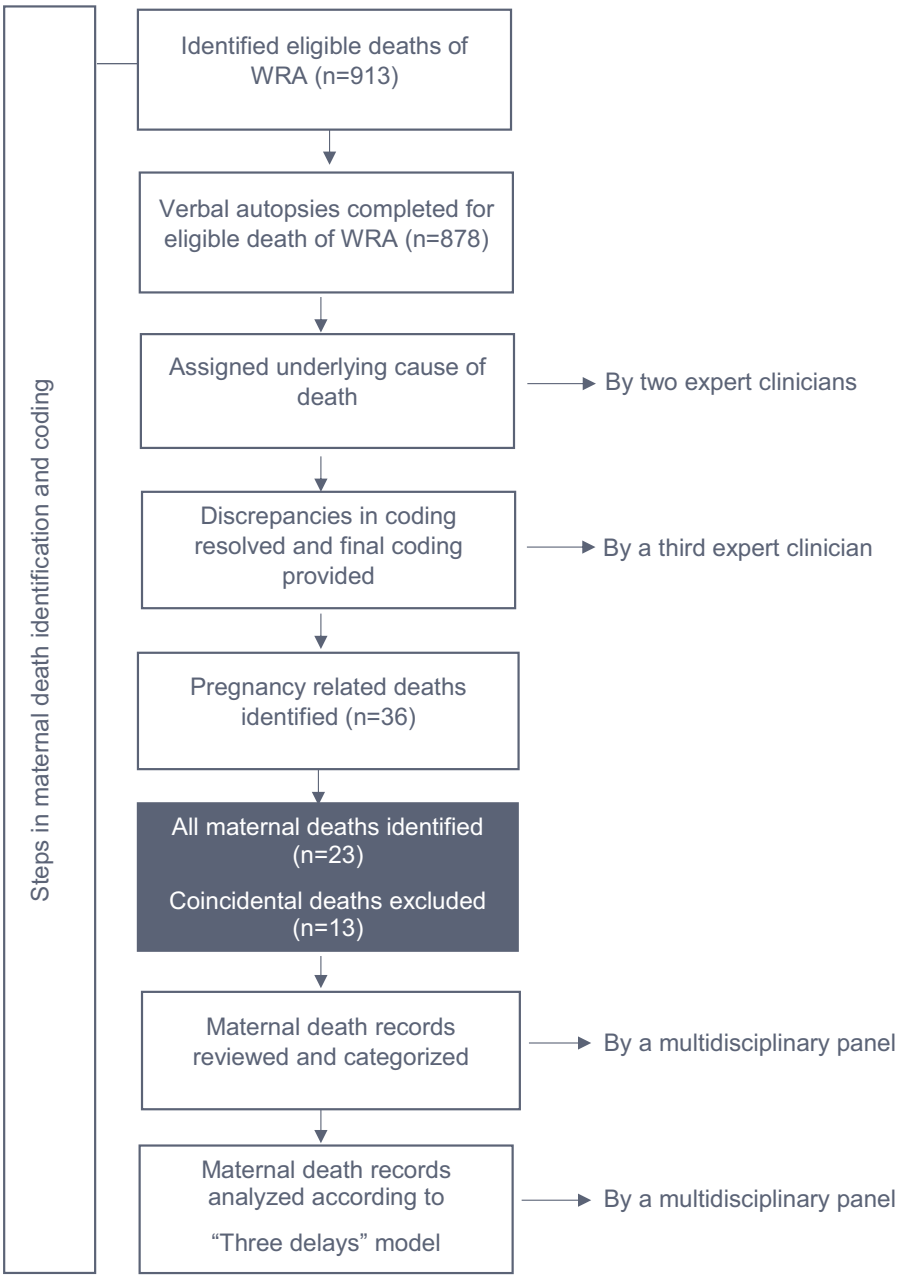

Figure 1 Maternal death identification and coding, Georgia, 2012.

causes (13), unrelated to pregnancy, were due to transport and other accidents (n=6), cancer (n=6) and liver cirrhosis.

Selected Characteristics of Women in Relation Causes of Mortality

The study showed that the majority (over 50%) of maternal deaths were among women aged 21–30 years. Importantly, the number of deceased women delivered by cesarean section was twice as high compared to vaginal deliveries (eight and four, respectively). As many as 26% (n=6) of deaths occurred post-abortion or from ectopic pregnancy. These included early fetal loss (three miscarriages) and two induced abortions, one from a self-attempted termination. Finally, 13% (n=5) of women were still pregnant at the time of death. Women who died from sepsis and embolism tended to deliver by cesarean section and were younger (range 21–30) as compared to the older age groups (Table 1).

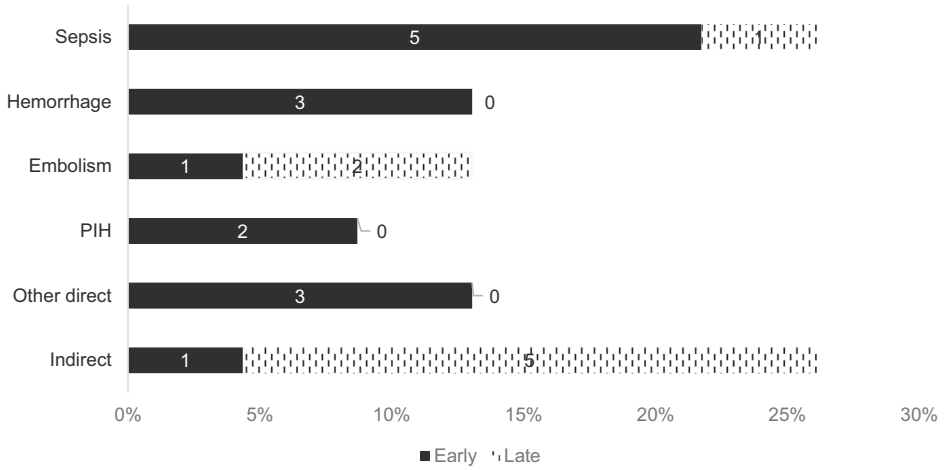

Figure 2 Causes of maternal deaths by time of death, Georgia, 2012.

Overview of Care

Overall, we found that suboptimal care was provided in 13 (87%) out of 15 early maternal deaths. Similarly, improvements in care which would have made a difference to the outcome in two (67%) of the three late maternal deaths due to direct obstetric causes.

Early Recognition and Appropriate Management

Our study found that delayed recognition of a severe or life-threatening condition was a significant problem. Out of the 23 cases of maternal death, only one (4%) was identified in a timely way. The other 16 (70%) were detected with delays and for six (26%) indirect deaths, timely identification of the problem was not a relevant factor. Along with delayed recognition, deficiencies were evident in the management of complications in many death cases (65%) (Figure 3).

There were delays in recognizing all sepsis cases (five were early and one was a late death). A significant problem identified was timely recognition of the clinical signs suggestive of infection (Table 2: case 4, case 9 and case 16). Some of the cases (eg case 16, Table 2) evidenced a delay in both timely recognition and treatment of sepsis. Medical records were deficient in half of the sepsis cases, which were missing a full set of vital parameters on day

Table 1 Selected Characteristics of 23 Maternal Deaths by Main Cause of Death (in Columns), Georgia, 2012

Characteristics	Sepsis/Septic Shock (n=6)	Obstetric Hemorrhage (n=3)	Embolism (n=3)	Preeclampsia/ Eclampsia (n=2)	Other Direct (n=3)	Indirect (n=6)	All (n=23)
Age, years							
21–30	4	1	2		2	3	12
31–40	2	1	1	1		2	7
≧40		1		1	1	1	4
Delivery mode							
Miscarriage/ectopic pregnancy	1	2				1	4
Induced abortion	1					1	2
Vaginal delivery	1	1	1			1	4
Caesarean delivery	3		2		1	2	8
Undelivered/pregnant				2	2	1	5
Time of death							
Antepartum				2	2	1	5
Post-abortion	2	2				2	6
Postpartum	4	1	3		1	3	12

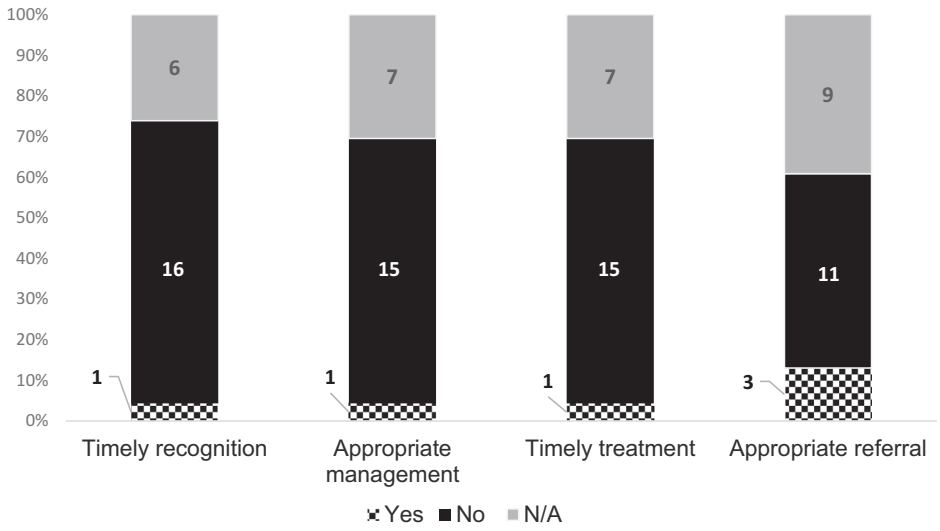

Figure 3 Evaluation of care provided to 23 deceased women by key characteristics, Georgia, 2012.

preceding to or at a time when the diagnoses of infection was made. Additionally, gaps were documented in timing and spectrum of laboratory testing. No blood or other samples were drawn for bacterial culture for presumed infection in five out of six sepsis cases. Although antibiotic therapy was initiated in most cases on the same day as infection was suspected, the delays and use of a proper antibiotic regimen was a significant problem.

Poor management was identified in all three fatal cases of obstetric hemorrhage. The management did not follow any of three basic principles of patient safety: the right patient, the right place, and the right procedure (case 3, Table 2). Although the uterine perforation was detected on time, the curettage was initially performed in a facility where complications could not be properly managed. The woman was transported to another specialized facility without prior stabilization. Her condition deteriorated during transportation. Stabilization measures also were inadequate in the referral hospital. A total hysterectomy was then performed instead of repairing the hole in the posterior wall of the uterus.

In one case of hemorrhage after a spontaneous abortion at mid-pregnancy (case 5, Table 2), the team misinterpreted the clinical signs as bleeding from a cervical laceration. A hysterectomy was conducted too late and failed to save the woman's life.

Similarly, we identified inadequate management of postpartum uterine atony (case 11, Table 2). Initial blood loss was underestimated. Surgical management and hysterectomy were delayed, and insufficient blood transfusion was applied, despite hemodynamic instability (with a hemoglobin of 50 g/L, and hematocrit of 6.8%).

Poor prophylaxis and management were evident in two of three cases of thromboembolic maternal deaths but had probably no association with the last case due to the time lag of 133 days (case 2 and case 17, Table 2).

Finally, in-depth clinical audit disclosed substantial deficiencies in preeclampsia management. Two women who died from severe preeclampsia had inadequate monitoring of blood pressure and lack effective antihypertensive treatment. Conversely, another woman (case 6, Table 2) received a loading intravenous overdose of magnesium sulfate (10g instead of the recommended 4g). This woman's condition deteriorated within one hour after the toxic dose suggestive of hypermagnesemia.

Maternal Referral

Along with deficiencies in early recognition and management of maternal complications, the study documented inappropriate and/or delayed referral in 11 (79%) out of 14 cases requiring referral (Figure 2). In six cases of early maternal deaths, the women were not referred in a timely manner or were referred to inappropriate level facilities.

Discussion

Our study is among the first analyzing the magnitude and pattern of both early and late maternal deaths in Georgia during 2012. Of the eight late maternal deaths identified in the present study, most (7/8: 88%) were unrecognized by the official statistics as maternal deaths. Direct cause of

Table 2 Individual Overview of Maternal Deaths (n=23), Georgia, 2012

Case #	Timing of Death	Brief History*	Cause of Death	Timely Recognition	Appr. Management	Timely Treatment	Appr. Referral	Quality of Care**
1	Early Maternal	31–40 years old, P1. Admitted to hospital at 18 GW, incomplete abortion. Self-administration of 10 tablets of Misoprostol (Cytotec©) to terminate pregnancy. Refused hospitalization, later due to aggravation of clinical condition, self-referred to the hospital. Curettage of uterine cavity 15 minutes after admission; antibiotics and saline infusion initiated. Developed septic shock, resuscitation started, hysterectomy performed. Condition deteriorated rapidly during the surgery, and she died.	Sepsis/septic shock	No	No	No	No	3
2	Early Maternal	21–30 years old, P0. Admitted to maternity hospital: 39 GW, severe preeclampsia, obesity, uterine fibroids, intrauterine fetal growth restriction, cephalic presentation, in the first stage of labor. CS performed 7 hours after admission upon woman's request. Discharged on the 4th day after delivery in satisfactory condition. On the 5th day after delivery, sudden death at home.	Embolism	No	No	No	Yes	3
3	Early Maternal	≥ 40 years old, P2. Admitted to hospital at 14 GW, incomplete abortion. Curettage of the uterine cavity. Postoperative hemorrhage - suspected uterus perforation. Saline infusion started. Woman transported to the district hospital. At admission acceptable circulation, mentally altered, Hb-52 g/L, Ht-7.6%. Total hysterectomy performed 20 minutes after admission. Infusion with 9000 mL Crystalloids, 2 packs of fresh-frozen plasma. At the end of the surgery: Hb-36g/L, Ht-3.5%. Woman died despite resuscitation performed.	Obstetric hemorrhage	Yes	No	No	No	3
4	Early Maternal	21–30 years old, P0. Admitted to maternity hospital: 38 GW, cephalic presentation, first stage of labor, pre-labor rupture of membranes. CS performed 50 minutes after admission upon woman's request. Antibiotic therapy initiated immediately after CS. Two days postpartum fever, no laboratory tests performed, antibiotic therapy continued. On day five fever persisted, laboratory tests performed, antibiotic regimen changed. Septic shock developed on day eight; patient died shortly after the shock.	Sepsis/septic shock	No	No	No	No	3

(*Continued*)

Table 2 (Continued).

Case #	Timing of Death	Brief History*	Cause of Death	Timely Recognition	Appr. Management	Timely Treatment	Appr. Referral	Quality of Care**
5	Early Maternal	31–40 years-old, P2. Admitted to hospital at 18 GW, spontaneous abortion. Treatment initiated with Oxytocin, macerated fetus spontaneously delivered. Curettage of the uterine cavity performed, bleeding started during the procedure. 10 IU of Oxytocin administered I/M. Bleeding continued. Transfusion of saline solution along with 20 IU Oxytocin. Fresh and frozen plasma transfused. Bleeding continued, hysterectomy performed after 5 hours. Post-operatively condition deteriorated, despite resuscitation measures died 12 hours post-surgery.	Obstetric hemorrhage	No	No	No	No	3
6	Early Maternal	≥ 40 years old, P4. Admitted to maternity hospital at 32 GW, essential hypertension. At admission: blood pressure (BP) 200/120 mmHg, proteinuria +2. No other laboratory tests performed. Bolus dose of Magnesium sulfate therapy started. One hour after Magnesium Sulphate injection, condition worsened. Overdose suspected. Patient died despite resuscitation measures.	Preeclampsia	No	No	No	Yes	3
7	Early Maternal	21–30 years old, P1. Admitted to maternity hospital at 39 GW, fetus in cephalic presentation, first stage of labor. Elective CS performed. Postoperative period uncomplicated. Discharged home in satisfactory condition. Re-admitted to hospital on day 5 after discharge with fever: 38.9°C, Pulse-124. Blood tests and abdominal ultrasound performed. Peritonitis diagnosed. Antibiotic therapy started. Hysterectomy performed. After the surgery, condition deteriorated further; she died 2 days later.	Sepsis/septic shock	No	No	No	No	3
8	Early Maternal	21–30 years old, P1. Admitted to maternity hospital at 16 GW, spontaneous abortion, fever 39°C; cervical dilatation. Fetus expulsed, curettage of uterine cavity performed. Antibiotic therapy initiated. After curettage condition worsened, septic shock diagnosed, and resuscitation initiated. Two days later the patient died.	Sepsis/septic shock	No	No	No	No	3

9	Early Maternal	31–40 years old, P3 Admitted postpartum to maternity hospital with fever (39° C). On day 9 after CS, discharged home, despite fever. Ultrasound examination performed, no laboratory tests. Antibiotic therapy prescribed and patient discharged home. Woman's condition worsened, re-admitted to hospital 8 days after discharge. Blood and urine tests performed, surgical site infection suspected; wound drainage conducted, but condition worsened further. Hysterectomy performed; the patient died shortly thereafter.	Sepsis/septic shock	No	No	No	No	3
10	Early Maternal	31–40 years old, P2. Self-referral at 33 GW to outpatient clinic with difficulty breathing and chest pain. BP 200/110 mmHg, no laboratory tests performed. Woman referred to district hospital within 1-hour after admission, condition deteriorated, and died despite resuscitation measures.	Preeclampsia/ Eclampsia	No	No	No	No	3
11	Early Maternal	21–30 years old, P0. Admitted in active labor, 41 GW, following an uncomplicated pregnancy. Normal progress in labor and delivery of a 4200-gram neonate. After placenta expulsion, 1 hour after delivery the patient developed atonic uterine bleeding. Uterotonics administered: Oxytocin 5 IU bolus dose and 10 IU diluted in 500 mL saline. BP 100/70, pulse 90. Transfusion of crystalloids commenced. After a short pause, the bleeding continued. Hysterectomy and resuscitation measures performed. Woman died shortly after surgery.	Postpartum Hemorrhage	No	No	No	N/A	3
12	Early Maternal	21–30 years old, P0. Admitted at 23–24 GW to referral hospital unconscious. Reportedly woman had not felt fetal movements in a week. IUFD confirmed at the first point of contact, at the district hospital. Antibiotic treatment initiated. Induction of labor. Four hours later, the patient's condition deteriorated. Pulse 120, BP 90/60, she developed respiratory distress. Woman transported to referral hospital and died shortly afterward.	Complication following intrauterine death.	No	Yes	Yes	No	2
13	Early Maternal	21–30 years old, P0. Elective CS at term. Esophageal intubation, final peri-arrest intubation. The patient suffered a cardiac arrest and died.	Complication of anesthesia/Failed Intubation	No	No	No	Yes	3
14	Early Maternal	>40 years old, multipara. Sudden death at home whilst 8 weeks GA. No autopsy.	Undefined(Sudden death at home)	N/A	N/A	N/A	N/A	N/A
15	Early Maternal	21–30 years old, P0. Admitted at 24 GW to referral hospital in altered mental status, fever, preceding otitis media with outpatient antibiotic treatment. Cranial CT on admission, laboratory tests, and antibiotic treatment initiated, developed coma and died within 24 hours.	Bacterial meningoencephalitis	No	No	No	Yes	3

(*Continued*)

Table 2 (Continued).

Case #	Timing of Death	Brief History*	Cause of Death	Timely Recognition	Appr. Management	Timely Treatment	Appr. Referral	Quality of Care**
16	Late Maternal	21–30 years old, P0. Admitted to referral hospital, 54 days postpartum after vaginal delivery, unconscious, transferred from district hospital with diagnosis of septic shock. Two admissions and discharges prior to transfer to referral hospital. Antibiotic therapy, hysterectomy performed in district hospital. Despite resuscitation measures, the woman died three days later.	Sepsis	No	No	No	Yes	3
17	Late Maternal	31–40 years old, P2. Died at home, 133 days after CS.	Embolism	N/A	N/A	N/A	N/A	3
18	Late Maternal	21–30 years old woman, P0. Died at home, 116 days after vaginal delivery.	Embolism	N/A	N/A	N/A	N/A	N/A
19	Late Maternal	21–30 years old, previous parity unknown. Admitted at 8 GW to hospital for vaginal bleeding, incomplete abortion. Vacuum aspiration performed. Re-admitted after 2 days with abdominal pain, ultrasound investigation confirmed ruptured ectopic pregnancy. Surgery performed and discharged from hospital in satisfactory condition. Died 69 days afterwards in intensive care unit treated for leukemia.	Myeloid leukemia	N/A	N/A	N/A	N/A	N/A
20	Late Maternal	21–30 years old woman, P1. Died 46 days after CS, in the ambulance during transfer to hospital. Prior to pregnancy, treatment of active tuberculosis. Three weeks of complaints: shortness of breath and fatigue.	Tuberculosis	No	No	No	N/A	3
21	Late Maternal	31–40 years old. Diagnosed with breast cancer during pregnancy. Initiated treatment after delivery, died in the hospital 186 days postpartum.	Breast cancer	N/A	N/A	N/A	N/A	N/A
22	Late Maternal	Woman ≥ 40-years old, previous parity unknown. Died at home 90 days after an abortion. Curettage performed at 12 weeks of gestation. History of breast cancer treatment. Diagnosed with recurrent breast cancer during pregnancy.	Breast cancer	N/A	N/A	N/A	N/A	N/A
23	Late Maternal	31–40 years old, Previous parity unknown. Died 167 days after vaginal delivery. Committed suicide, no known history or treatment for mental health disorders.	Suicide	No	N/A	N/A	N/A	N/A

Notes: *For the purpose of anonymization, only previous parity (not gravidity) and age categories are provided. **1 – good care; 2 – improvements of care which would have made no difference to the outcome, and 3 – improvements of care which would have made a difference to the outcome.

Notes: *For the purpose of anonymization, only previous parity (not gravidity) and age categories are provided. **1 – good care; 2 – improvements of care which would have made no difference to the outcome, and 3 – improvements of care which would have made a difference to the outcome.

Abbreviations: P0, nulliparous prior to present pregnancy; P1- 1, delivery prior to present pregnancy; CS, cesarean section; GW, gestational weeks; Hb, hemoglobin; Ht, hematocrit; CT, computer tomography; IUFD, intrauterine fetal death; N/A, not available.

one officially reported late maternal death following ectopic pregnancy was reclassified as indirect only after the comprehensive case review, while other late maternal deaths were misclassified in other ICD-10 chapters.

With the introduction of an electronic notification system, it is noteworthy that the remarkable progress has been achieved in Georgia in death registration coverage, and the death certification process has improved. However, despite well documented improvements, the quality of cause-of-death certification and coding has still been overlooked by Georgia's vital registration system. Most pregnancy checkboxes remain empty within one year postpartum following a maternal death. This study's association between death and pregnancy was made possible only through data matching or birth records linkage. The coupling of pregnancy and female deaths is particularly challenging with deaths occurring during pregnancy, after abortion, or any deaths due to indirect obstetric causes. Official statistics systems have not captured late maternal death in many countries who have conducted confidential enquiries, including Denmark, Ireland, Finland, and the UK.[23] Our study confirms that the complications of pregnancy and birth may surpass 42 days postpartum. It underscores the importance of monitoring, proper classification and the integration of late maternal death into official statistics.

Most of the late maternal deaths documented in our study were indirect, with the leading cause being malignant neoplasms. This finding is in line with a prior study from Italy, where cancer was a leading cause of late maternal deaths, occurring in 38.8%.[13] Another indirect cause of late maternal death was tuberculosis. The outcome for pregnant women with tuberculosis is poorer, with a six-fold increase in the risk of maternal mortality.[24] Treatment adherence in previous treatment episodes was the cause of an ensuing maternal death from tuberculosis in our study. While the proportion of successfully treated patients with tuberculosis has improved markedly among new cases, Georgia still has a high percentage (27%) of clinical failure or poor treatment adherence in previous tuberculosis treatment episodes.[25] Overall, critical aspects of care among the late maternal deaths were indicative of deficiencies in preconception care in Georgia, where an improvement might have prevented or limited some maternal deaths. Preconception care provides critical opportunities to detect and manage chronic diseases and other health risks, and better protect the health of women with non-communicable as well as communicable diseases and their offspring.

In addition to identifying the causes of maternal death, the individual death audits provide important insights into the organization and delivery of maternal health services in Georgia. Overall, the study showed deficiencies and delays at all stages of provision of care. While analyzing a third delay (ie delivery of adequate care within the health facility), we assessed the care at the first admission to a facility and at the referral hospital, including timely recognition, appropriate management and treatment delay, and any delays in transfer to another higher-level facility. Lack of effective and timely care at any of these time points may aggravate a patient's condition and result in a poor outcome.[26–29] In most of the reviewed cases, we found either delays in referral, referral to a facility not capable of providing the required level of care, or both. For example, facilities that managed the miscarriages and related complications, such as bleeding and uterus perforation leading to maternal death, were basic maternity units with limited capacity to handle such complications or to stabilize the patient before referring to another facility.

We found substandard care in which improvements would have made a difference to the outcome in 13 (87%) of early and two (67%) of the three late maternal deaths from direct obstetric causes. The findings are in line with UK confidential enquiries to maternal deaths and studies from Netherlands which identified that improvements in care would have made a difference to outcomes for over 90% of women who died.[30,31]

Sepsis or septic shock was the most common underlying direct cause of maternal deaths in Georgia in 2012. Substandard care wherein improvements could have made a difference to the outcome was found across all sepsis cases. Delay in recognition and diagnosis of sepsis was responsible for majority of maternal deaths from sepsis documented by our study. This agrees with findings from other countries.[32] Achieving a low sepsis-associated mortality is based on rapid triage using a risk-scoring system and early therapy, including appropriate antibiotic treatment within one hour of a suspected diagnosis.[33,34] As such, obstetricians should maintain a higher level of alert and provide information to pregnant and postpartum women on the importance of seeking timely medical care. Moreover, the best care for sepsis is multidisciplinary; that is, where different specialists are involved in case management at early stage of case identification.[17] A multidisciplinary approach should become a standard of care for Georgia as well, in addition to wide-scale adherence to basic principles of patient care; namely,

regular measuring, monitoring and recording of full spectrum of vital parameters, and strict infection control. In line with some other studies,[35,36] we found more maternal sepsis among younger women and in women delivered by caesarean section. Post-operative infection was the source of sepsis in our study, while respiratory infections were dominant sepsis cases in the maternal health studies from the high-income countries.[3]

Inadequate antibacterial prevention and/or timely treatment was the main element of substandard care we found by our study. Routine antibiotic use prior to the initiation of or during caesarean section is recommended for women undergoing caesarean section.[20] No antibiotic prophylaxis was provided in either of the three women who delivered via caesarean section and who died from sepsis or septic shock. The medical records review of these women does not provide evidence of clinical signs of sepsis prior to the surgery. Our data point to the fact that sepsis represents a major threat to maternal health in Georgia, and that there is frequently late recognition then suboptimal care. Thus, improvements in this area are urgent.

Whilst the number of women who died from pregnancy induced hypertension was low in our study, substandard care was evident for these women. Important opportunities are present to further improve care, prevent deaths and reduce morbidity from pregnancy induced hypertension. Identifying women with risk factors[21] is important for early recognition as well as proper antenatal care, referral, and appropriate management. In our study, risk factors were present in both cases of preeclampsia. However, no increased schedule of antenatal care for these women with pre-existing hypertension was provided, and no visits were scheduled between 28 and 33 weeks of gestation. This is too long a time period without medical contact for the high-risk women.

In Georgia, a full assessment for pre-eclampsia or HELLP syndrome, including a spectrum of blood tests, is strongly recommended in women presenting with symptoms or signs of this syndrome. Yet, in our study, neither woman received proper laboratory tests, imaging investigations or treatment, according to the national clinical practice guidelines. Poor compliance with evidence-based clinical practice guidelines and protocols, as demonstrated by our study, remains a challenge in Georgia and across many countries. Multi-faceted, tailored solutions, going beyond simple dissemination of guidelines/protocols should be extensively implemented by Georgia to increase compliance with existing evidence-based protocols. Some European countries, such as UK and Norway, which began implementing targeted interventions to lower avoidable maternal mortality over the last decade, have reached 10-fold reductions in deaths from pre-eclampsia and eclampsia or have achieved a zero level of maternal deaths from preeclampsia. Maternal death inquiries of previous years in these countries identified substandard care of hypertensive complications.[4,37,38]

Pregnancy and particularly the delivery mode by cesarean section increases the risk of thromboembolism, further aggravated in the immediate postpartum period. Thromboembolism was the third major cause of maternal deaths in our study. We identified substandard care in at least two of the three maternal deaths due to thromboembolism. Suggested preventive interventions include early pregnancy and postpartum risk assessment for thromboembolism and thromboprophylaxis with low-molecular weight heparin after cesarean delivery in women with risk factors (other than previous venous thromboembolism or thrombophilia).[18,19] Most importantly, timely referral is recommended for all pregnant or postpartum women who complain of newly emerged dyspnea, for evaluation of thromboembolism or pulmonary embolism.[18]

Delay in the diagnoses and adequate management of maternal hemorrhage are important substandard care factors that may lead to severe maternal morbidity or death.[39] Several studies have found that most deaths from hemorrhage are preventable.[7,40,41] Early recognition and adequate assessment of blood loss in the management of obstetric hemorrhage is the cornerstone of care. In our study, blood loss was significantly underestimated in all three maternal deaths from hemorrhage. In addition, the clinical management did not comply with the national clinical practice guidelines. In the case of major obstetric hemorrhage, there should be no delay in surgical management. While no other surgical management procedures were used before opting for hysterectomy, all three women in our study underwent delayed hysterectomy. The strategies for blood transfusion also were inadequate. Furthermore, the risk of postpartum hemorrhage can be reduced by 60% with active management of the third stage of labor and routine administration of prophylactic uterotonic drugs immediately after delivery.[22] Despite strong recommendations in force, there is still a significant variation in uterotonic drug practices in Georgia.

The bundle approach[42–44] recently has been proposed as an intervention to address suboptimal adherence to hemorrhage and other clinical practice guidelines and to

improve the quality of care. Further, staff education and simulation exercises could help to improve accuracy of the blood loss measurement.[45,46] Unfortunately, no quality of care improvement strategies or continuous medical education and audits with multidisciplinary morbidity and mortality reviews were required or implemented by health facilities in Georgia at the time of the study period.

Our findings from Georgia highlight the need for improvements in quality of obstetric care to reduce maternal deaths. Since 2015, several initiatives have been implemented to reduce avoidable maternal deaths. These initiatives include in-service training courses for obstetrician-gynecologists, midwives and intensive care specialists and the updating of national clinical practice guidelines. Health systems improvements have been implemented. They aim to regionalize specialized maternal and newborn care services and create a coordinated system of care between different facility levels. These efforts led to improvements in facility infrastructures, scope of practice and definition of competencies at each level along with a greatly strengthened referral system. Further acceleration of these initiatives and systemic changes to improve the quality of care offer a strong hope of decreasing in preventable maternal mortality.

One of the strengths of our study lays in the opportunity to interview family members to get the details of each patient's case and thus providing a reliable clinical timeline prior to the maternal death. The study was also strengthened by a comprehensive methodology likely to include all deaths within a year of abortion and non-facility deaths, with no or less likely missing number of deaths of WRA within a year following delivery. The study also had the advantage of being able to access and use data from hospitalizations during pregnancy and one year before the fatal event. However, the study did not include a detailed review of medical records or characteristics of care for late maternal deaths due to indirect causes. Additionally, postmortem autopsies -important to examine the cause and factors that contribute to death[47] - were not performed in any of the 23 maternal death cases, due mainly to cultural challenges related with postmortem autopsy practices in Georgian society.

Conclusions

Most maternal deaths which were analyzed in this study were potentially preventable. The clear implication is that improvements in the quality of care are necessary to reduce maternal mortality. While we recognize that evaluation of substandard care may lack robustness, the cases of maternal mortality in our study illustrate the presence of failures in quality of care such as delayed and misdiagnoses, inadequate treatment, failure to follow national protocols and delays or inappropriate referrals to manage obstetric emergencies. Comprehensive, multi-dimensional, proactive strategies are of paramount importance to implement efforts to address these challenges and to minimize preventable maternal deaths. Recommended actions include: (1) routine periodic national analyses and monitoring of maternal deaths; (2) establishing an internal (facility-based) clinical audit system to guide the design of obstetric interventions and policies; (3) enhancing active surveillance for identification and registration of late maternal deaths; (4) improving routine postpartum care focusing on early recognition of complications to reduce late maternal deaths; (5) introducing a mandatory continuous medical education system; (6) implementing quality improvement initiatives to address modifiable risk factors; and (7) introducing mechanisms to reward quality and safety of maternity care, including financial incentives for measured quality of care and public reporting of healthcare quality data.

Ethics

The study was conducted in accordance with the Helsinki Declaration.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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Norwegian Summary

Vi har studert dødsårsaker hos kvinner i reproduktiv alder i Georgia og byrden av maternelle lidelser i den totale dødelighetsraten (Studie I). Livsstil sykdommer er den største trusselen for kvinners helse i fertil alder. Kreft er den ledende døds-årsaken med brystkreft som den viktigste kreft-typen. Deretter følger skader/uhell og hjerte-karsykdom. Dette understreker et sterkt behov for å ta i bruk livsløp- og helse-systemrespons, og multi-sektorielle tilnærming for å dempe epidemiene av livsstilssykdommer.

Vi har også studert årsaker til og nivå av underrapportering av mødre-dødelighet (Studie II) og identifisert de viktigste årsakene til i suboptimal fødselshjelp for tidlige og sene mødre-dødsfall (studie III). Studien viste en 39 % underrapportering av mødre-dødsfall i den offisielle statistikken. Sene og indirekte dødsfall var hyppigste under-rapportert. De fire viktigste årsakene til maternell død var sepsis, blødning, lungeemboli og svangerskapsforgiftning. Suboptimal omsorg ble dokumentert i 87 % av tidlige og 67 % sene mødre-dødsfall.

De fleste kjente årsaker til mødre-dødsfall kan forebygges eller behandles med optimalisert klinisk intervensjon og korrekt timing. Dette krever imidlertid tilgang til behandling på riktig nivå før, under og etter fødselen.

Vi observerte en reduksjon av mødre dødsfall i Georgia i perioden. Hvis denne trenden skal fortsette kreves ytterligere forbedring i kvalitet og sikkerhet på flere nivåer i helsesystemet.