The association of prepregnancy body mass index and changes of prepregnancy BMI/ body weight between pregnancies with risk of preeclampsia: a birth registry study from Tanzania

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Abstract

Objective

Preeclampsia is among the three leading causes of maternal mortality and morbidity worldwide, occurs in 6-8% of all pregnancies, and is estimated to account for at least nine percent of maternal deaths in Africa. Studies from developed countries show that high prepregnancy BMI increases the risk of preeclampsia. We examined the association of prepregnancy body mass index and changes of prepregnancy body weight between pregnancies with risk of preeclampsia in the second pregnancy. In the term *preeclampsia* we also include cases of eclampsia.

Method

A historic registry based study was used, analysing births registered in the Kilimanjaro Christian Medical Center (KCMC) birth registry between July 2000 and May 2013. Two sets of data were analysed; singleton births of gravida 1 or 2 mothers (n= 17, 750 births), and the linked first two recorded singleton births to a woman, irrespective of gravidity (n =3, 595 mothers). Prepregnancy BMI was categorized according to WHO categories underweight (less than 18.5), normal (18.5 – 24.9), overweight (25.0 – 29.9) and obese (30 or greater). Measured confounders were adjusted for in multivariable models.

Results

Among the 17,750 singleton births, 9.1 % of the mothers were underweight, 24.0 % were overweight, and 7.4 % were obese. Five hundred and eighty-two pregnancies (3.3 %) were affected by preeclampsia. Compared to women of normal BMI, overweight and obese women had an increased risk of preeclampsia (AOR 1.5 (95%CI 1.2 – 1.7 and, 1.7(1.2 – 2.1), respectively, while underweight was protective (AOR 0.8 (0.8 - 1.1). Among 3,595 mothers without preeclampsia in their first recorded pregnancy, incidence of preeclampsia was 2% in

the second recorded pregnancy. Weight loss, but not weight gain between the pregnancies was associated with risk of preeclampsia in the last pregnancy. The effect of weight change did not change after adjustment for BMI in second pregnancy.

Conclusion

The association between prepregnancy body mass index and preeclampsia in this population of pregnant women in Northern Tanzania corresponds with earlier findings from developed countries. Overweight and obesity should be considered an obstetric risk factor is this population.

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Abbreviations

ACOG – American college of obstetricians and gynaecologists

ANC – Antenatal clinic

AOR – Adjusted odds ratio

BMI – Body mass index

CI – Confidence interval

CIH – Centre for international health

HELLP – Haemolysis electrolyte liver enzyme

IUGR – Intrauterine growth restriction/retardation

KCMC – Kilimanjaro Christian Medical Centre

MDG – Millennium development goals

NIMR – National institute for medical research

SPSS – Statistical package for social sciences

WHO – World health organization

UIB – University of Bergen

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1.0 General introduction

Definition of preeclampsia and eclampsia

Hypertension is defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; or systolic blood pressure increase of ≥30 mm Hg or diastolic blood pressure increase of ≥15 mm Hg [1]. Pre-eclampsia is defined as hypertension accompanied by proteinuria first detected after 20 weeks of gestation. Proteinuria is defined as at least 300 mg protein in a 24 hour urine collection (or ≥ 1 + dipstick (30 mg/dL) in a single urine sample [2]. Preeclampsia can further be defined as mild or severe; mild preeclampsia defined as elevated blood pressure of systolic blood pressure of >140mm Hg or diastolic blood pressure > 90 mmHg taken 6 hours apart combined with protenuria of 300 mg from a 24 hours urine collection [3]. Severe preeclampsia defined as more elevated blood pressure accompanied with end organ damage [3]. Preeclampsia may develop into a more severe condition called eclampsia. Eclampsia refers to the development of grand mal seizures in a woman with gestational hypertension or preeclampsia [4]. The seizures can occur before delivery, during, or after labor. It is a serious condition that is associated with increased risk of mortality and morbidity in the pregnant women and poor perinatal outcomes. For the developing countries the mortality associated with this manifestation is as high as 15% [4].

Classification of hypertensive disorders during pregnancy

There are four levels of hypertensive disorders during pregnancy, defined by blood pressure, proteinuria and severity of symptoms: *Gestational hypertension/ pregnancy induced hypertension* defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg diagnosed for the first time after 20 weeks' gestation, in the absence of proteinuria and resolves within three months post-delivery [5]. *Preeclampsia* defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg diagnosed for the first time

after 20 weeks' gestation, accompanied by proteinuria. Preeclampsia can be mild without proteinuria and symptoms of severity and can be severe with blood pressure of equal or more than 160/110mm Hg with or without proteinuria. *Eclampsia* is the occurrence of grand mal seizures occurred as a complication of pre-eclampsia [5]. Chronic hypertension defined as hypertension diagnosed before 20 weeks of gestation or having hypertension before present pregnancy which can be with no underlying causes or with underlying disease. *Superimposed preeclampsia* defined as having higher blood pressure than before pregnancy in a known chronic hypertensive women followed by significant or worsening proteinuria (with or without symptoms of severity) [5].

Signs and symptoms of preeclampsia

These include high blood pressure and presence of protein in the urine, epigastric pain, vomiting, sudden severe swelling of hands, face or feet, and hyperreflexia. Laboratory abnormalities may include hemolysis, elevated liver enzymes, low platelet counts (HELLP syndrome) and increased of serum creatinine [6]. Some women may present with convulsions, abdominal pain or general malaise. Headache and visual disturbances are the signs of central nervous system involvement [7].

Risk factors

Risk factors for preeclampsia have been well documented [8-10]. These include nulliparous, advanced maternal age, race other than white, high body mass index (BMI), chronic hypertension, diabetes (I/II), previous preeclampsia, previous intrauterine growth restriction (IUGR), previous abruption of placenta, long time since previous pregnancy, multiple pregnancy and triplet gestation, change in paternity from previous pregnancy, systemic inflammation and preexisting hypertension, diabetes mellitus, insulin resistance and renal diseases [6]

Etiology of preeclampsia

The pathogenesis of preeclampsia is still unknown, but genetic, immunologic, and environmental factors have been reported to be involved in the etiology, either separately or by interacting. Some studies have reported that preeclampsia is a two-stage disease that includes abnormal placentation [11]. The first stage is without symptoms where placenta insufficiency occurs as a result of development of abnormal placenta during the first trimester, and this is accompanied by release of excessive amounts of placental materials into the maternal circulation. This is followed by second stage which includes symptoms where in the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the HELLP syndrome (hemolysis, elevated liver function enzymes and low platelets), eclampsia, and other end-organ damage.

Preeclampsia detection and prevention

Early detection is necessary to prevent severe damage to the woman and the fetus and to prepare for a safe delivery. In developed countries, the procedures for detection of preeclampsia are well elaborated. However, most clinical and laboratory tests reported to be useful in the early detection of preeclampsia remain unrealistic and cost-effective particularly in developing countries [12]. Uterine Doppler artery and maternal serum makers have been reported to show promise in the early detection of preeclampsia, but there is not enough evidence to support their clinical use in poor resource settings [13]. Aspirin therapy used as prophylaxis was reported to be beneficial in decreasing preeclampsia in the specific population and to recommend its widespread needs more research [14, 15]. Similarly calcium supplementation was recommended to be used to those with highest risk and women who needs calcium supplementation [15, 16]. Vitamins supplementation, commonly C and E, was disproved by WHO studies [17]

Complications of preeclampsia

Preeclampsia is associated with several maternal complications which include eclampsia, ischemic or hemorrhagic stroke, hemolysis, liver damage, and thrombocytopenia (HELLP syndrome with or without hemorrhage), disseminated intravascular coagulation, liver hemorrhage/rupture, pulmonary edema, adult respiratory distress syndrome, acute renal failure and death [4].

Treatment and management of preeclampsia

Management of preeclampsia mainly involves either delivery or observation depending on gestational age and severity of the syndrome. Studies have shown that delivery of the baby and placenta is the only cure, but the maternal and fetal risks have to be balanced. Delivery can be good for the safety of the mother but not for the very premature baby [18]. Decision on delivery and expectant management should be based on the assessment of fetal gestational age, fetal status and maternal condition. Close observation can be appropriate to women with mild preeclampsia and gestational age below 34 weeks [19]. A policy of expectant management can be applied in the management of severe preeclampsia with viable fetus and gestational age below 34 weeks with close monitoring of uncontrolled high blood pressure, increased maternal organ dysfunction and signs of fetal development [19]. On the other hand prolonged gestational age with severe preeclampsia can lead to fetal death or asphyxia and increased risk of maternal death [18]. Similarly, women with eclamptic seizures should be stabilized first using magnesium sulphate followed by delivery in a timely manner [19]. Antihypertensive drugs can be used as well to lower the blood pressure and prevent fetal bradycardia. Corticosteroids for lung maturation and magnesium sulphate for prevention of seizures can be administered to women with severe preeclampsia or eclampsia [18]. Mode of delivery for preeclamptic women should depend on fetal gestation age and condition, fetal presentation, presence of labour, and bishop score of the cervix [18]. Management during

labour and delivery should aim at prevention of seizures or eclampsia and control of hypertension, and women should be monitored up to 24 hours post-delivery [18].

Limitations in the management of preeclampsia

Studies have shown that proper management of preeclampsia depends on functional health systems which provide timely access to health care. This is in contrast to most of the developing countries in Sub-Saharan Africa including Tanzania, where access to health have been documented to be limited by a number of reasons, as described in the "Three Delays Model" [20-22]. First, delay in the decision to seek care in which a woman lacks proper information of when to seek help and where she can get help [23]. This has been reported to be associated with social demographic factors including lack of knowledge, single mothers and marital status [24]. Increasing user fee, poverty and lack of decision making have shown to worsen the situation [25, 26]. Second, delay in reaching the health facility has been documented to be among the obstacles in decreasing maternal mortality rate in developing countries [20]. This includes transportation with poor infrastructure especially during rainy season and referral system in which those who lives in rural area are the most affected compared to their counterpart [22, 25]. Unequal distribution of health facilities which favour urban compared to rural is among the obstacles [21, 22]. Third, delay in the provision of health services which can be contributed to a number of factors including shortage of health care providers, lack of drugs and incompetent staff who can sometime fail to administer some drugs like magnesium sulphate [20, 21]

1.1 Global burden of preeclampsia

Eight hundred women die every day from pregnancy or child birth related complications worldwide [27]. Approximately 10 -20 million women will experience complications associated with child bearing each year [26]. Ninety nine percent of these deaths occur in developing countries [27]. The differences in numbers of maternal deaths in parts of the world reflect inequities to access of health services and the gap between rich and poor [26]. In developing countries the maternal mortality ratio is 240 per 100,000 compared to 16 per 100,000 in developed countries [27]. There are large disparities between countries, within countries, people with low and high income and between rural and urban areas [28]. Approximately 80% of maternal deaths are contributed by direct causes which include severe bleeding mostly after birth, infections commonly post-delivery, hypertensive disorders during pregnancy including preeclampsia, and unsafe abortion. The remaining 20% are due to previous existing disease like malaria.

Worldwide, 10-15% of direct causes of maternal death are estimated to be due to preeclampsia [29]. Preeclampsia is among the 3 leading causes of maternal mortality and morbidity worldwide, occurs in 6-8% of all pregnancies and accounting for at least 9.1% of maternal death in Africa [30]. Worldwide, it is approximated that over 4 million women will develop hypertensive disorders during pregnancy every year, in which 50.000-100.000 women will die from preeclampsia each year, and the disorder will be responsible for approximately 300.000 perinatal deaths [27, 31].

1.2 Maternal mortality in developing countries

Sub-Saharan Africa is responsible for 50% of all the maternal deaths globally [32], of which 70% – 80 % are associated with direct causes which include complications of pregnancy, delivery, labour and postpartum period [30]. In Sub-Saharan Africa case fatality related to

pregnancy induced hypertensive disorders has been reported to range from 3% to 23% [22]. In resource limited settings where early diagnosis and obstetric management are deficient, preeclampsia can be the leading cause of maternal and fetal morbidity and mortality [33, 34]. Worldwide, the incidence of preeclampsia is estimated to range from 2% to 10 % [31]. In developing countries the reported prevalence of preeclampsia ranges from 1.8% to 16.7% [20]. The wide variation in reported prevalence likely reflects variations in data collection or study design. The majority of maternal deaths are preventable [27]. Most of these deaths are due to lack of prenatal care, lack of access to hospital care, lack of resources, inappropriate diagnosis and poor management [29]. The focus of millennium development goal number five is to reduce maternal mortality by three quarters by 2015. This has been a challenge for developing countries in which maternal mortality is 100-200 higher than in developed countries [29]. Preeclampsia has been reported to increase the number of maternal deaths by 1.8% in developed countries and by 14% in developing countries [35].

1.3 Maternal deaths in Tanzania

Tanzania has been reported to be among the countries with higher maternal mortality rate with a challenge of meeting fifth millennium development goal in 2015 [27]. Despite a high coverage of women who attended at least one ANC visit [36], Tanzania had been in a two different trends of maternal mortality ratio, from 1961 to 2010 [21]. After independence 1961 to 1990 maternal mortality ratio had a downward trend from 453 to 200 per 100,000 live births, and again increased up to 578 per 100,000 live births from 1990. However, from 2010 maternal mortality ratio in Tanzania has remained 454 deaths per 100,000 live births [21]. A woman dies almost every hour from maternal causes in Tanzania [27].

1.4 Preeclampsia in Tanzania

Preeclampsia and associated complications have been reported to be among the main causes of maternal deaths in Tanzania. A study conducted in Dar es Salaam found eclampsia as a

complication from preeclampsia accounted for 12 % of all maternal deaths and was the third most common cause after haemorrhage and abortion [36]. The case fatality rate for hypertensive disorders during pregnancy including eclampsia in different populations among Tanzanian has been reported to range from 5% to 7.8% [36, 37], in contrast to a case fatality rate of 1% or less in high income countries [29]. A study at KCMC on maternal deaths conducted with data from medical birth registry from 2000 – 2007 found a maternal mortality ratio of 550/100,000, and hypertensive disorders during pregnancy was reported to be the leading cause contributing to 41 out of the 119 deaths [38].

1.5 Preeclampsia and obesity

The risk of preeclampsia increases with increasing pre-pregnancy body mass index (BMI) [10, 39]. BMI is widely accepted as a measure of both overweight and underweight. The World Health Organization classifies BMI into four categories, namely: underweight 16-18.5kg/m2, normal 18.5-25kg/m2, overweight 25–29.9 kg/m2 and obese > 30 kg/m2. In many populations, prevalence of obesity among the pregnant population has been reported to increase significantly over the last decade. This has negative effects on many aspects of female reproductive life included preeclampsia [40]. Also increase in prepregnancy BMI from one pregnancy to a next pregnancy has been reported to increase the risk of preeclampsia [41]. Moreover, weight gain beyond normal during pregnancy is associated with an increased risk of pre-eclampsia in the subsequent pregnancy [8].

Overweight and obesity in pregnancy have also been associated with an increased risk of other maternal complications such as gestational hypertension, macrosomia, induction of labour and caesarean delivery as well as an increased risk of neonatal complications [42]. On the other hand, underweight increases the risk of preterm delivery, low birth weight and

anaemia, but lowers the risk of pre-eclampsia, gestational diabetes, obstetric intervention and post-partum hemorrhage [42].

Obesity is a serious global public health problem and has consequences for nearly all areas of medicine. Obesity has been reported to increase the risk of preeclampsia about 3 fold [43] and is the leading identified attributable risk for this disorder. In obstetrics, obesity not only has a direct implication on the health of a pregnant woman but also on the offspring's weight during infancy and beyond. As such, maternal weight may influence the prevalence and severity of obesity in future generations [44]. Pregnancy has been identified as a key time to target a weight control or weight loss strategy to help curb the rapidly growing obesity epidemic [45].

1.6 Obesity in Tanzania

Also the prevalence of obesity among women of reproductive age in Tanzania has been increasing significantly during the last decades [46]. The Tanzania demographic health survey (TDHS) conducted in 2010 found the overall prevalence of overweight and obesity among women of reproductive age has increased from 18% and 4% in year 2004/2005 to 21.1% and 6.1% in year 2010, respectively [46, 47]. Another population based study from Dar Es Salaam, Tanzania, showed that the prevalence of obesity has increased from 3.6% to 9.1% among women of reproductive age between 1995 and 2004 [48]. Compared to other regions in Tanzania, overweight and obesity among women of reproductive age in Kilimanjaro has been reported to be even higher 24.1% and 10.8% respectively [46]. We were not able to identify more recent studies on prevalence of overweight and obesity in women of reproductive age in Tanzania

2.0 Statement of the problem and justification of the study

Millennium development goal number five aims to reduce maternal deaths by three quarter by 2015. The most efficient method for preventing maternal death is to focus on well-known preventable causes of maternal deaths, of which deaths due to preeclampsia are among the most important.

At KCMC, hypertensive disorders during pregnancy including preeclampsia were reported to be a leading cause of maternal death. While obesity is an established risk factor for developing preeclampsia in developed countries, few studies from low and middle income countries have reported on obesity and pregnancy. Given the background of poverty and malnutrition among African women, the impact of pre-pregnancy BMI related with risk of pre-eclampsia may be of different from women in the high income countries. We aimed to examine the association of prepregnancy BMI and changes of prepregnancy BMI/body weight between pregnancies on the risk of preeclampsia in a population of pregnant women in Northern Tanzania. Dissemination of the findings from this study may give clinicians an overview of the health problems related to obesity and pregnancy induced hypertensive disorders in this population

3.0 Study goal

The main goal of this study is to contribute to the improvement of management of preeclampsia by examining the importance of prepregnancy BMI and changes in prepregnancy BMI/body weight between pregnancies in relation to preeclampsia. In our study we include eclampsia cases when we refer to the term *preeclampsia*.

3.1 Study objectives

Broad objective

The general objective of this study is to investigate the effect of prepregnancy BMI and changes in prepregnancy BMI/body weight between pregnancies on risk of preeclampsia.

Specific objective

1. To compare maternal sociodemographic and obstetric characteristics according to pre-pregnancy BMI categories in first and second pregnancy.
2. To estimate the distribution of maternal characteristics in relation to preeclampsia in first and second pregnancy.
3. To assess the effect of pre-pregnancy BMI on preeclampsia in the different BMI categories.
4. To assess change in pre-pregnancy BMI/body weight between pregnancies on the risk of preeclampsia in second pregnancy.

4.0 Methodology

Study setting, design and population

Study setting

According to the national census 2012 [49], Tanzania has 30 administrative regions divided into 169 districts. Kilimanjaro is one of the regions and is divided into 7 districts, namely Moshi rural, Moshi municipal (urban), Mwanga, Same, Hai, Siha, and Rombo. Kilimanjaro region lies in the northern part of Tanzania, boarded by Kenya in north and east, Tanga region in south, Manyara region in south-west and Arusha region in west.

The population of Kilimanjaro region is approximately 1,640,000 people with 793,000 males and 846,000 females [49]. The Moshi municipal district had a population of 184,292, Moshi rural 466,737, Mwanga 131,442, Same 269,807, Hai 210,533, Siha 116,313 and Rombo 260,963.

The current study was conducted at Kilimanjaro Christian Medical Centre which is situated in Moshi municipal district. The Kilimanjaro Christian Medical Center (KCMC) is a private hospital. The two main ethnic groups in Kilimanjaro are Indigenous Chagga which is the third largest ethnic group in Tanzania and followed by Pare. There are also other small ethnic groups which have migrated to nearby Kilimanjaro such as the Kahe and Masai tribe. KCMC is one of the four zone referral hospitals in Tanzania. The hospital has different departments including obstetric department which receives women from the local communities as well as referred women from other regions. The hospital has 450 beds, and as a tertiary care hospital it serves a population of more than 11 million. The medical birth registry at KCMC was established in collaboration with researchers at the Department of Global Public Health and Primary Care (formerly Department of Public Health and Primary Health Care) at the University of Bergen Norway, and has been in operation since July 2000.

This hospital was chosen for this study because of the following reasons. (1) It is the only hospital in this region which has birth registry system. (2) Midwives from this hospital have been trained on how to conduct interviews using standard questionnare. (3) It has been documented from previous studies that hypertensive disorders during pregnancy were the leading cause of maternal death in this hospital.

Study design

This is a registry based study using information singleton pregnancies to gravida one or two women whose data were collected at the time of each delivery. The data were prospectively collected by obstetricians and midwives from all women who delivered at Kilimanjaro Christian Medical Centre from July 2000 to May 2013.

Study population

Our source population included mothers who delivered at Kilimanjaro Christian Medical Centre (KCMC) from July 2000 to May 2013 and whose reproductive history data were entered into the medical birth registry. The mothers' records are linked to their children's records using a unique maternal hospital number assigned for each woman who deliver at KCMC for the first time. A total of 46,030 deliveries were recorded. To analyse the effect of prepregnancy BMI on the risk of preeclampsia we included women who delivered singleton birth at first or second pregnancies while excluding other gravidities. To analyse the effect change in prepregnancy BMI/body weight between pregnancies on the risk of preeclampsia in the second pregnancy we included a woman's first two singleton deliveries, irrespective of gravidity.

Data collection

Data collectors from this study were midwives from the obstetric unit who were trained for two days. Along with this, one secretary was trained as data entry before the commencement of this project. The medical birth registry information is collected from all mothers who

deliver at KCMC. Midwives conduct the interview using a standardized questionnaire for all mothers within 24 hours after delivery, or later in case a mother had complications. The interviews were done on a daily basis including public holidays and weekends. Abstracted data from files relating to each mother written by obstetricians were also included. In addition, mothers admitted to the hospital were asked to provide their antenatal (ANC) cards for more clarification regarding their pregnancy records including pre pregnancy weight and height. Verbal informed consent was obtained from each mother prior to the interview, and a unique maternal hospital identification number was used to protect confidentiality. The details of data collected during interview are shown in questionnaire **(Appendix 1).** In summary, the information collected during interview and through inspection of medical files includes parents' social-demographic characteristics, reproductive history, pregnancy and birth characteristics such as; maternal health before pregnancy, maternal health during pregnancy, and complications during labour and delivery, and new born health status. This information was then entered into a computerized data base system. The quality checks and validation of the birth registry information was done in 2004/2005 and the manual with definitions and detailed explanation was written and accessed in 2005 [50].

The analyses are based on two sets of data; a set of first and second pregnancies where each pregnancy was the unit of analysis ("birth record" analysis, and a set of maternally-linked pregnancies where each mother was represented with two pregnancies and where the mother was the unit of analysis ("record linkage analysis"). Birth record analysis includes objectives 1 – 3, whereas record linkage analysis includes objective 4. An overview of the birth record and the record linkage analysis is presented in **Table 1**.

Inclusion criteria

In the birth record analysis we included mothers who had pre-pregnancy body weight and height recorded and who delivered their first or second singleton birth at KCMC at any time

between July 2000 and May 2013. In the record linkage analysis we included a woman's first two singleton births at KCMC, irrespective of gravidity.

Exclusion criteria

For objectives 1-3 we excluded women with multiple gestations, women who were referred from the rural area for various medical reasons, and those with missing information on the BMI variables. Our final sample consisted of 17,750 singleton births for the birth record analysis **(Figure 2).** For objective 4, in addition to the exclusion criteria of birth record analysis, we also excluded mothers whose information did not match between year of birth and mother's age and women with preeclampsia in the first pregnancy. However, we included mothers who had only one valid measurement of maternal height. Our final sample consisted of 3,595 women in the record linkage analysis **(Figure 3).**

Study variables

Outcome variables: For all objectives our outcome was preeclampsia, defined as gestational hypertension of at least 140/90 mmHg measured on two separate occasions =≥4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine, arising after the 20th week of gestation in a previously normotensive woman. This definition of preeclampsia is in accordance with World health organisation, and includes mild, moderate and severe preeclampsia. For simplicity we use the term *preeclampsia*. In the analysis of change in prepregnancy BMI/body weight between pregnancies our outcome was incidence (%) of preeclampsia in the second pregnancy.

Explanatory variable: In the birth record analysis (objectives 1 – 3) our main exposure variable was pre-pregnancy BMI based on self-reported maternal prepregnancy weight in kilograms and documented height in centimetres from ANC visits. Lower and upper cut-off points for height were set at 130 cm and 200 cm, respectively. Lower and upper cut-off points for body weight were set at 35 kg and 120 kg, respectively. BMI was calculated as body

weight in kg/height in metres squared, and we accepted BMI values between 15 and 40. We excluded records with BMI above 40 (0.4%) and BMI below 15 (0.5%). We categorized BMI according to WHO definitions as underweight ≤18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.

In the birth record analysis we included sociodemographic variables (mother's age, mother's education, antenatal care visits, marital status, mother's occupation, mother's tribe, and mother's height,) categorised as in **Table 2a**. To assess whether effects of BMI were similar across maternal height categories (below 164 cm and 165 cm or more) and across gestational age categories (below 37 completed weeks and 37 completed weeks or more, and missing) the results were stratified. We also performed tests for interaction by adding an interaction term between BMI and maternal height or gestational age, in the model.

In the record linkage analysis (objective 4) our exposure variables were change in pre-pregnancy BMI or change in body weight between the woman's first and the second pregnancy. Normal BMI was used as a reference group. Change in pre-pregnancy body weight was calculated by subtracting the body weight recorded in the second pregnancy from that in the first pregnancy (weight2-weight1) and categorised á priori into gained ≥ 10 kg, gained 5-9.9 kg, less than 5 kg change, lost 5-9.9 kg and lost ≥10 kg. Normal weight in both pregnancies was used as a reference. We tested for interaction between BMI in second pregnancy (linear), and BMI change.

In all analyses, variables were entered into the multivariable model if they were associated with preeclampsia with a p-value less than 0.1 in the univariate analysis. In general, records with missing values were included only in the descriptive analysis of the participant characteristics. Since for each variable in the multivariable model the proportion of missing values was less than 1%, individuals with missing values on any independent variable were

not included in the model. In the analysis where we stratified for gestational age, missing gestational age (8.1%) was analysed as a separate category.

Data analysis

Data were extracted from Microsoft Access data base and then transferred to Statistical Package for Social Science (SPSS) version 20 for Windows for analysis, then followed by data cleaning. Descriptive analysis including means and proportion were calculated. To assess the statistical associations Pearson Chi-squres statistics test were used to compare categorical variables across BMI categories. The significance level was set at p=0.05, with 95% as the preferred confidence interval. P for trend was calculated and reported for ordinal variables. Binary and multivariable logistic regression analysis was performed to assess the strength of association between dependent and independent/explanatory variables while adjusting for potential confounders; mother's age, mother's education, mother's body height, pre pregnancy body mass index, and mother's tribe. Adjusted odds ratios with 95% confidence intervals were reported.

Ethical issues

Ethical clearance

The ethical approval was sought from Kilimanjaro Christian Medical University College research ethics committee prior the commencement of this study **(Appendix 2).** Also the birth registry at KCMC had ethical clearance from the Tanzania national institute for medical research (NIMR) 2003 **(Appendix 3)**, and from the Regional Ethical Committee (Health Region III) in Norway 1999 **(Appendix 4).** To every enrolee, the research study, its goal and benefit was clearly explained and this was followed by orally consent. Participation was on voluntary basis and mothers were taught to be free to disagree to be interviewed if they wished to do so. There was no penalty if they decided not to be interviewed, and their decision would not affect the provision of appropriate care and management. Confidentiality

was guaranteed during the interview process. The completed questionnaires were kept in a secure place and only accessible by the research team.

5.0 Discussion on methods

Discussion of this thesis includes literature on definition, classification, risk factors, aetiology, complications and management of preeclampsia. Further literature on obesity and BMI, most articles published from 2000 to 2013. Key terms were preeclampsia, eclampsia, obesity, BMI, pregnancy, developing countries, Tanzania and Kilimanjaro. The literatures were retrieved from Google Scholar, Cochrane Database of Systematic Reviews and PubMed (MEDLINE).

Design

This study was a historic cohort study, and the design should be appropriate for the study question, because we set out to examine the association of prepregnancy BMI and changes of pre-pregnancy BMI/body weight on risk of preeclampsia. Our study is based on existing registry data and we did not perform any sample size computations. We consider the following as methodological challenges in this study.

5.1 Methodological Challenges

Internal validity

Internal validity refers to the degree to which the data measure what is intended to measure [51]. Bias refers to the lack of internal validity [52]. Bias is a systematic error which can be encountered in sample selection and data collection [51].

Internal validity depends on the presence of information bias, selection bias, or confounding.

Information Bias

Information bias is a distortion in the measure of association caused by inaccurate information. It is mostly occur during data collection [52]. The most common type of information bias is misclassification bias which refers to specificity and sensitivity of the test/procedure used to identify the exposure and effect/outcome. Differential misclassification occurs when the misclassification is different between the groups which are compared, for

example that misclassification in exposure differs between those who have the outcome and those who not have the outcome. We have non differential misclassification if misclassification is similar across the groups which are compared. Although using a standardized questionnare during interview is the most effective method in gathering high quality information, in our study there is a possibility for less accuracy of the respondents to recall events such as body weight before pregnancy, last normal menstrual period etc. To minimize error in the collection of information, data collectors were trained, the standardized questionnaire was piloted before the data collection started, and in year 2005 the registry produced an instruction manual which further improved quality of data [50]

Selection Bias

Selection bias is a systematic error resulting from sample selection [51]. Since KCMC is a referral hospital receiving complicated pregnancies, there is a likelihood of overestimating measures of diseases. Approximately 86.7% of women give birth at health facility in Kilimanjaro region. To minimize selection bias, we excluded women who were referred from the rural area for medical reasons such as complications in current or previous pregnancies.

Loss to follow up has been reported to be important in follow up studies. To our understanding, we agree there is a challenge of identifying subsequent deliveries of the same women. KCMC being a referral hospital in which women can be referred for one pregnancy and the second birth delivered to her nearby health facility she lives. Therefore to link reproductive health/ outcome and mother's birth we used a unique identification number, while excluding women who were having mismatched information between year of birth and maternal age, however women who were lost in subsequent birth might have different characteristics and therefore these results cannot be generalised to them.

Confounding

Observational studies may be affected by confounders [52]. A confounder is a third factor which correlates with both dependent and independent variables. Confounding can be controlled/ minimized during study plan by matching or restriction, and during analysis by stratification, matched analysis or multivariable analysis. In both analyses we restricted our sample to singleton birth by excluding multiple pregnancies. In addition we performed multivariable adjustment to control of confounders.

External validity

External validity refers to which degree the results obtained from one population can be projected to the rest of that population/other settings. Moreover external validity goes together with internal validity though the presence of internal validity does not guarantee the external validity [51]. The distribution of characteristics of women who delivered in this setting might be different from those who delivered outside KCMC. For example, home deliveries in the Kilimanjaro region are approximated to be 12% [46].

Therefore, generalization of the results needs to be taken with precaution.

Recommendations and policy implications

The association of prepregnancy obesity with risk of preeclampsia in this population corresponds with earlier findings from developed countries. Midwife should counsel pregnant women on the consequences associated with high prepregnancy weight. Health authority in Tanzania should recognize obesity among pregnant women as a growing health problem.

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7.0 Article

Comment: The article was initially planned to fulfil the regulations for a Master thesis in international health, where two articles were required. The regulations later on changed to one article (reference: A GUIDE FOR STUDENTS AND SUPERVISORS ON WRITING A THESIS FOR: **THE DEGREE *MASTER OF PHILOSOPHY IN INTERNATIONAL HEALTH.* & THE DEGREE *MASTER OF PHILOSOPHY IN ORAL SCIENCES*** *(This document has been adapted and partly rewritten from a similar document developed by the tropEd network, revised by the Programme Committee for Master's at CIH 13th January 2014).*

The association of prepregnancy body mass index and changes of prepregnancy BMI/ body weight between pregnancies with risk of preeclampsia: a birth registry study from Tanzania

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Abstract

Objective

Preeclampsia is among the three leading causes of maternal mortality and morbidity worldwide, occurs in 6-8% of all pregnancies, and is estimated to account for at least nine percent of maternal deaths in Africa. Studies from developed countries show that high prepregnancy BMI increases the risk of preeclampsia. We examined **1.** The effect of prepregnancy BMI and **2.** Changes of prepregnancy BMI/body weight between pregnancies, on the risk of preeclampsia in the second pregnancy. In the term preeclampsia we also include cases of eclampsia.

Method

A historic hospital registry study design was used, analysing births registered in the Kilimanjaro Christian Medical Center (KCMC) birth registry between July 2000 and May 2013. Two sets of data were analysed; singleton births of gravida 1 or 2 mothers (n= 17, 750 births), and the linked first two recorded singleton births to a woman, irrespective of gravidity (n =3, 595 mothers). Prepregnancy BMI was categorized according to WHO categories underweight (less than 18.5), normal (18.5 – 24.9), overweight (25.0 – 29.9) and obese (30 or more). Measured confounders were adjusted for in the multivariable model.

Results

Among the 17,750 singleton births, 9.1 % of the mothers were underweight, 24.0 % were overweight, and 7.4 % were obese. Five hundred and eighty-two pregnancies (3.3 %) were affected by preeclampsia. Compared to women of normal BMI, overweight and obesity was associated with risk of preeclampsia (AOR 1.5 (95%CI 1.2 – 1.7 and, 1.7(1.2 – 2.1), respectively, while underweight was protective (AOR 0.8 (0.8 - 1.1). Among the 3,595 mothers with linked pregnancies, incidence of preeclampsia was 2% in the second recorded

pregnancy. Weight loss, but not weight gain between pregnancies was associated with an increased risk of preeclampsia in the second pregnancy. The effect of weight change between pregnancies was not related to BMI per se.

Conclusion

Pre pregnancy maternal overweight or obesity increased the risk of preeclampsia. Both weight loss and weight gain from one pregnancy to a next pregnancy increased the risk of preeclampsia, although not statistically significant for weight gain. Overweight and obesity among pregnant women should be considered as a challenge also in developing countries.

Keywords: Preeclampsia, eclampsia, obesity, BMI, pregnancy, developing countries, birth registry, Kilimanjaro and Tanzania.

Introduction

Globally it has been estimated more than 287,000 women die each year due to pregnancy related causes [1]. Complications of pregnancy and childbirth are the leading cause of death amongst women of reproductive age. The majority of maternal deaths occur in developing countries including Tanzania [2]. Worldwide, 10-15% of direct causes of maternal death are estimated to be due to preeclampsia [3]. The focus of millennium development goal number five is to reduce maternal mortality by three quarters by 2015. This has been a challenge for developing countries in which maternal mortality is 100-200 higher than in developed countries [3]. Ten percent of all pregnancies are affected by hypertension, of which 2 to 8% are complicated by preeclampsia [3, 4]. Preeclampsia has been reported to increase the risk of maternal mortality by 1.8% in developed countries and by 14% in developing countries

Preeclampsia is a multi-system disease, and is characterized by systolic blood pressure of >=140mm Hg and diastolic blood pressure of >= 90 on at least two occasions in four hours

apart after 20 weeks of gestation in a previously normotensive woman, combined with proteinuria [5-7]. The etiology of preeclampsia is still unknown although the following factors have been reported to play a role: the placenta, genes, the immune response, and maternal vascular disease [3]. Duley et al further explained that endothelial dysfunction from poor blood supply to the placenta accounts for the secondary changes in maternal target systems such as vasoconstriction which is responsible for the signs and symptoms of preeclampsia. There is no efficient treatment of preeclampsia rather than symptomatic management since the cause is unclear [4]. Preeclampsia is associated with several complications which include eclampsia, ischemic or hemorrhagic stroke, abruptio placentae, hemolysis, liver damage, and thrombocytopenia (HELLP syndrome with or without hemorrhage), disseminated intravascular coagulation, liver hemorrhage/rupture, pulmonary edema, adult respiratory distress syndrome, acute renal failure and death [8]. Eclampsia is the presence of convulsions in any woman who has preeclampsia, or then presents with, hypertension in pregnancy of any cause [9].

Risk factors for preeclampsia have been well documented [10-12]. These include nulliparity, advanced maternal age, race other than white, high body mass index (BMI), chronic hypertension, diabetes (I/II), previous preeclampsia, previous intrauterine growth restriction (IUGR), previous abruptio placenta, long time since previous pregnancy, multiple pregnancies and previous stillbirth. The risk of preeclampsia is associated with a raised pre-pregnancy BMI [12]. The association between risk of pre-eclampsia and increase in BMI between two pregnancies have been reported [13]. Moreover, both obesity and overweight during pregnancy are associated with an increased risk of pre-eclampsia in the subsequent pregnancy [10].

Obesity is a serious global public health problem and has consequences for nearly all areas of medicine. Obesity has been reported to increase the risk of preeclampsia about 3 fold and is the leading identified attributable risk for this disorder. In obstetrics, obesity not only has a direct implication for the health of a pregnant woman but also has impact on the offspring's weight during infancy and beyond. As such, maternal weight may influence the prevalence and severity of obesity in future generations. In many populations the prevalence of obesity among pregnant women has been reported to increase significantly over the decade, and this has negative effect on many aspects of female reproductive life included preeclampsia [13]. Pregnancy has been identified as a key period to target a weight control or weight loss strategy to help curb the rapidly growing obesity epidemic [14].

A study among US women by Getahun and his colleagues [10] revealed that the risk of preeclampsia increased with increasing BMI between pregnancies. BMI is widely accepted as a measure of both overweight and underweight [15]. Overweight and obesity in pregnancy have been associated with an increased risk of different maternal complications including pre-eclampsia whereas babies born to these women are at increased risk of neonatal complications [16]. On the other hand, underweight increases the risk of preterm delivery, low birth weight and anaemia, but lowers the risk of pre-eclampsia, gestational diabetes, obstetric intervention and post-partum hemorrhage [14].

Few studies from low and middle income countries have reported on obesity and pregnancy. In a study of women of reproductive age in South Asia [17] revealed that there is an increase of overweight and obesity among women of this age group. Also the rate of obesity among women of reproductive age in Tanzania has been increasing significantly [18]. A Demographic Health Survey from the years 2004 and 2005 conducted in Tanzania found that the prevalence of overweight and obese among women of reproductive age was 18% and 4%,

respectively [18]. A population based study from Dar Es Salaam, Tanzania, shows that the prevalence of obesity among women of reproductive age has increased progressively from 3.6% to 9.1% between 1995 and 2004 [19]. We were not able to identify more recent studies on prevalence of overweight and obesity in women of reproductive age in Tanzania. Most of the studies regarding the effect of maternal pre-pregnancy BMI and changes of pre-pregnancy BMI on risk of pre-eclampsia in subsequent pregnancies have been done in high income countries. There is scarce information on this important topic in low income countries. We aimed to examine **1)** The effect of prepregnancy BMI and **2)** Changes of prepregnancy BMI/body weight between pregnancies on the risk of preeclampsia in the second pregnancy.

Materials and methods

This study was conducted at Kilimanjaro Christian Medical Center (KCMC), which is a private hospital based in Moshi urban district, Kilimanjaro region in Northern Tanzania **(Figure 1).** According to census 2012 the region has a population of 1,640,087 [20]. The two main ethnic groups in Kilimanjaro are Indigenous Chagga which is the third largest ethnic group in Tanzania and followed by Pare. There are also other small ethnic groups which have migrated to nearby Kilimanjaro such as the Kahe and Masai tribe. KCMC is one of the four zone referral hospitals in Tanzania. The hospital has different departments including an obstetric department which receives women from the local communities as well as referred women from other regions. The hospital has 450 beds, and as a tertiary care hospital it serves a population of more than 11 million. The medical birth registry at KCMC was established in collaboration with researchers at the Department of Global Public Health and Primary Care (formerly Department of Public Health and Primary Health Care) at the University of Bergen Norway, and has been in operation since July 2000.

This is a hospital registry study. Our source population included mothers who delivered at Kilimanjaro Christian Medical Centre (KCMC) from July 2000 to May 2013 and whose reproductive history data were entered into the medical birth registry. The mother's records are linked to their children's records using a unique maternal hospital number assigned for each woman who deliver at KCMC for the first time. A total of 46,030 deliveries were recorded.

The data were prospectively collected by obstetricians and midwives from all women who delivered at Kilimanjaro Christian Medical Centre from July 2000 to May 2013. The medical birth registry information is collected from all mothers who deliver at KCMC. Trained nurse midwives conduct the interview using a standardized questionnaire for all mothers within 24 hours after delivery, or later in case a mother had complications. The interviews were done on a daily basis including public holidays and weekends. Abstracted data from files relating to each mother written by obstetricians were also included. In addition, mothers admitted to the hospital were asked to provide their antenatal (ANC) cards for more clarification regarding their pregnancy records including pre pregnancy weight and height. Verbal informed consent was obtained from each mother prior to the interview, and a unique maternal hospital identification number was used to protect confidentiality. The details of data collected during interview are shown in questionnaire **(Appendix 1).** In summary, the information collected during interview and through inspection of medical files includes parents' social-demographic characteristics, reproductive history, pregnancy and birth characteristics such as; maternal health before pregnancy, maternal health during pregnancy, and complications during labour and delivery, and new born health status. Data were extracted from a Microsoft Access data base and then transferred to Statistical Package for Social Science (SPSS) version 20 for Windows for analysis.

The analyses are based on two sets of data; a set of first and second pregnancies where each pregnancy was the unit of analysis ("birth record analysis", and a set of maternally-linked pregnancies where each mother was represented with two pregnancies and where the mother was the unit of analysis (" record linkage analysis"). Birth record analysis includes objectives 1 – 3, whereas record linkage analysis includes objective 4. An overview of the birth record and the record linkage analysis is presented in **Table 1**.

For objectives 1-3 we studied women who delivered their first or second singleton birth at KCMC between July 2000 and May 2013. We excluded multiple births, women who were referred from the rural area for medical reasons, and those with missing information on the BMI variables. Our final analysis sample consisted of 17,750 singleton births **(Figure 2).**
For objective 4 we included a woman's first two singleton deliveries at KCMC between July 2000 and May 2013, irrespective of gravidity. In addition to the exclusion criteria as presented in Figure 2, we excluded mothers with preeclampsia in first recorded pregnancy and mothers whose information on year of childbirth and mother's age for the two pregnancies did not match. We included mothers who had at least one valid measurement of maternal height. The final sample consisted of 3595 mothers **(Figure 3).**

For all objectives our outcome was preeclampsia, defined as gestational hypertension of at least 140/90 mmHg measured on two separate occasions =≥4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine, arising after the 20th week of gestation in a previously normotensive woman. This definition of preeclampsia is in accordance with WHO, and includes mild, moderate and severe preeclampsia.
The main exposure variable for objectives 1-3 (birth record analysis) was pre-pregnancy BMI based on self-reported maternal prepregnancy weight in kilograms and maternal height in

centimetres from ANC visits. Lower and upper cut-off points for height were set at 130 cm and 200 cm, respectively. Lower and upper cut-off points for body weight were set at 35 kg and 120 kg, respectively. BMI was calculated as body weight in kg/height in metres squared, and we accepted BMI values between 15 and 40. We excluded records with BMI above 40 (0.4%) and BMI below 15 (0.5%). We categorized BMI according to WHO definitions as underweight ≤18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.

The main exposure variables for objective 4 (record linkage analysis) were change in pre-pregnancy BMI/body weight between the first and second recorded pregnancy. The BMI was categorised as described above. Change in prepregnancy body weight was calculated by subtracting the body weights measured at first ANC visits in connection with the two pregnancies (weight2-weight1). Normal weight in both pregnancies was used as a reference. We modelled weight change both in categories (gained 20-29.9 kg, gained 10-19.9 kg, gained 5-9.9 kg, less than 5 kg change, lost 5-9.9 kg, lost 10-19.9 kg, lost 20-29.9 kg) and as a continuous variable in kg. We defined categories á priori.

Descriptive statistics including means and proportions were calculated. Pearson Chi-square statistics was used to assess associations between BMI categories and categorical factors, and between preeclampsia and categorical factors. The significance level was set at $p = 0.05$. P for trend was computed for the ordinal variables like mother's BMI, mother's age, mother's education and mother's height. Binary and multivariable logistic regression analysis was performed to assess the strength of association between the dependent variable and independent variables. Unadjusted and adjusted odds ratios with 95% confidence intervals were reported.

For birth record analysis we included sociodemographic variables (mother's age, mother's education, antenatal care visits, marital status, mother's occupation, mother's tribe, and mother's height) as presented in **Table 2a** in the multivariable model. In a second step we included some potentially mediating factors in the multivariable model; chronic hypertension, diabetes mellitus, and heart diseases before pregnancy, to explore if the association between BMI and preeclampsia was explained by these factors. To assess whether effects of BMI were similar across maternal height categories (below 164 cm and 165 cm or more) and across gestational age categories (below 37 completed weeks and 37 completed weeks or more), we performed analyses stratified for maternal height and gestational age. We also tested for interaction by adding an interaction term between BMI and maternal height/gestational age in the model. For record linkage analysis we tested for interaction between BMI in a second pregnancy as a linear term and BMI change.

For objective 4, sociodemographic characteristics in second pregnancy (maternal age, education, prenatal care, marital status, and body mass index) were included in the multivariable model **Table 4.** Prepregnancy BMI in second pregnancy and effect on preeclampsia was analysed in a multivariate model in three steps **Table7**

In all analyses, variables were entered into the multivariable model if they were associated with preeclampsia with a p-value less than 0.1 in the univariate analysis. Records with missing values were included only in the descriptive analysis of the participant characteristics. Since for each variable in the multivariable model the proportion of missing values was less than 1%, individuals with missing values on any independent variable were not included in the model. In the analysis where we stratified for gestational age, missing gestational age (8.1%) was analysed as a separate category.

The ethical approval was sought from Kilimanjaro Christian Medical University College research ethics committee prior the commencement of this study **(Appendix 2).** Also the birth registry at KCMC had ethical clearance from the Tanzania national institute for medical research (NIMR) 2003 **(Appendix 3)** and from the Regional National Ethics committee (Health Region III) Norway 1999. **(Appendix 4)**

Results

Objectives 1 – 3 (birth record analysis)

In the analysis of 17, 750 first and second singleton births, overall prepregnancy mean BMI was 23.5, 9.1 % were underweight, 24.0 % were overweight and 7.4 % were obese **(Table 2a).** The highest mean BMI was found among mothers above 35 years of age, women who had the highest education, women with four or more ANC visits, married women, business women, professional women, Pare tribe and women who had body height between 155cm - 164cm. The highest proportion of underweight mothers was found among teenage mothers, mothers without education, mothers who were missing information on ANC visits, single mothers, mothers who were students during pregnancy, mothers who had body height above 165cm and women from other tribes apart from Chagga and Pare. The highest proportion of overweight and obese mothers was among mothers above 30 years of age, women with the highest education, mothers who attended four or more ANC visits, women who were married, business women, and women who had professional work.

Women having their second child and women with chronic hypertension and gestational hypertension or diabetes before pregnancy had a higher mean BMI and a higher proportion of overweight and obesity than women having their first child and women without chronic hypertension and gestational hypertension or diabetes **(Table 2b).** Being underweight was

most common among women with heart diseases before pregnancy (22.6 %), while obesity was most common among women with chronic hypertension (18.4 %) and diabetes before pregnancy (19.0 %).

Preeclampsia was recorded in five hundred and eighty-two pregnancies (3.3 %) **(Table 3).** The risk of preeclampsia increased with increasing mothers BMI, maternal age, maternal educational level, and body height (p-values for trend <0.05). Women with chronic hypertension, gestational hypertension or gestational diabetes, and women from the Pare tribe had a higher risk of preeclampsia than their counterparts. The risk of preeclampsia was 3.5% in first pregnancy and 3.0% in second pregnancy (data not presented on table).
In the adjusted analyses **(Table 3),** overweight and obese women were 1.5 and 1.7 times more likely to have preeclampsia than women with normal BMI (95 % CI 1.2-1.7 and 1.2–2.1, respectively), while underweight women were less likely to have preeclampsia (OR 0.8, 95% CI 0.6-1.1). Mother's age, height, tribe and marital status were still associated with pre-eclampsia after adjustment, and the trend was significant for prepregnancy BMI and mother's age. We further adjusted for potential mediators such as chronic hypertension, heart diseases and diabetes before pregnancy. The effect of BMI only slightly changed, with odds ratios for underweight, overweight and obese women 0.8, 1.4, and 1.6, respectively (data not presented in table).

We further stratified our data into gestational age less than 37 weeks (preterm) and 37 and more weeks (term) and tested for interaction between gestational age and BMI using BMI as a linear term (results not presented in a table). For completeness, also results for missing gestational age were included. The association between BMI and preeclampsia was stronger in term births than in preterm births (adjusted odds ratio 2.0 and 1.1, respectively, for obese

vs. normal), and p-value for trend was only significant in term births (0.188 in preterm births vs. ≤0.001 in term births). However, p-value for interaction was non-significant (0.18). We also tested for a possible interaction between mother's height and BMI using prepregnancy BMI as a linear term (results not shown in a table). The effect of BMI was stronger in woman below 165 cm than in woman above 165cm (adjusted OR 1.8 vs. 1.4) in the obese group. However the differences did not reach statistical significance, p value for interaction 0.53.

Objective 4 (record linkage analysis)

Table 4 describes sociodemographic characteristics in the second recorded pregnancy in relation to preeclampsia for the 3,595 women who were recorded with (at least) two singleton births. Only prepregnancy BMI was statistically associated with risk of preeclampsia.

The rate of preeclampsia in the second recorded pregnancy was 2% **(Table 5).** Mothers with normal BMI in both pregnancies were the largest category and formed the reference group. Women who had normal BMI in first pregnancy did not increase their risk of preeclampsia in second pregnancy if their BMI category changed to overweight or obese. Women who were overweight in both pregnancies did not have an increased risk of preeclampsia in second pregnancy, whereas women who were overweight in first pregnancy and obese in second pregnancy had an increased risk in second pregnancy (AOR 2.2). Interestingly, women who had normal BMI in first pregnancy and were underweight in second pregnancy had a high risk of preeclampsia; adjusted odds ratio 6.0 (1.7-21.5) although this is based on small numbers (37 women).

In a corresponding analysis of weight change between pregnancies **(Table 6)** we found high risk of preeclampsia both among women who lost weight (10 or more kg) and among women who gained weight (20 or more kg). P-value for trend was only significant among women who lost weight. We further analysed weight gained/lost as a continuous variable (in kilograms) in the multivariate model, where we found no statistically significant associations

(adjusted P value 0.797 for weight gain and 0.074 for weight loss) (results not presented in table).

Prepregnancy BMI in second pregnancy and effect on preeclampsia was analysed in a multivariate model in three steps **(Table 7**); first step in bivariate analysis, second step with covariates, and the third step with covariates and the weight change as categorical variable. In all three steps, obesity was associated with risk of preeclampsia (OR 2.3, 2.0, and 2.0 respectively, although not statistically significant in the last step). We also tested for interaction between BMI in second recorded pregnancy as a linear term with BMI change, where we found it is non-significant (P for interaction 0.421)

Discussion

Objectives 1 – 3 (birth record analysis)

Results from our study add to the increasing body of evidence which suggests that prepregnancy weight gain predispose women to preeclampsia. We found a positive association between higher body mass index and the risk of developing preeclampsia, gestational hypertension and chronic hypertension. Conversely, low BMI had a protective effect on preeclampsia.

Previous research has found a strong association between increasing BMI and preeclampsia [21]. Other studies have reported that the risk of preeclampsia increases rapidly from BMI values of 15-30 [22], we have found the same results. The prevalence of underweight, overweight and obese was found to be 9.1%, 24% and 7.4% respectively. A study on primary preeclampsia in the second pregnancy conducted by Getahun D et al [10] found a prevalence of 7.8%, 19.5% and 13.2% respectively. We found a 1.5 times higher risk of pre-eclampsia in

overweight (BMI 25.0-29.9 Kg/m2) and a 1.7 times higher risk in obese (BMI > 30 Kg/m2) to women who delivered singleton birth. Similarly Sohinee et al [23] found the risk of 1.7 and 3.1 among nulliparous women delivering singleton babies in Aberdeen. We also found a significantly lower risk of pre-eclampsia in underweight women (OR 0.8(95% CI 0.6 – 1.1)), a finding collaborated by Sohinee Bhattacharya et al [15]

Women of advanced maternal age were reported to have a higher occurrence of preeclampsia compared with the younger ones 6.5% vs. 2.8% and they were more likely to have an increased body mass index of ≥24kg/m2. Sohinee et al [24] reported similar findings that the risk of preeclampsia increased with increasing BMI. Older women were 2.3 times more likely to have preeclampsia compared to women under 35 years of age. The study of registry-based on primiparous women in Finland 1997-2008 reported similar increased risk [25]. Another study conducted among Brazilian population [2] concluded that women who were older with high BMI during pregnancy had a risk of hypertension disorders including preeclampsia compared to their counterpart.

Other researchers have reported gestational hypertension to be linked with an increasing maternal weight and risk of developing preeclampsia [26]. This association was also observed in this study.

We also reported preterm associated with increased risk of preeclampsia, whereas term birth was seen to have higher risk of preeclampsia compared to preterm birth. Women who were underweight had increased risk of preterm birth compared to women who were term (data not presented in the table). The findings collaborated by Ali Khatib et al [27]. Compared to women of normal BMI, obese women were more likely to have university education. This is

contrast with a study done by Chaturica et al [26] who reported obese women were less likely to obtain university knowledge than health weight women.

Objective 4 (record linkage analysis)

The risk of developing preeclampsia in the second pregnancy had a relationship with the prepregnancy BMI in the first pregnancy [10]. Getahun et al reported similar findings from his study which shows risk of preeclampsia in the second pregnancy depends not only on BMI in the present pregnancy, but also BMI in the previous pregnancy. Additionally his study showed the increased risk of preeclampsia when woman is overweight or obese in both pregnancies. We have observed the same findings. We also showed the association of decreased prepregnancy BMI and increased risk of preeclampsia, for example in those women who went from normal to underweight. This is contrast with the study done by Getahun et al [10] who revealed the decreased prepregnancy BMI reduced the risk of preeclampsia. Similarly women who gained 20kg or more between pregnancies were at increased risk of preeclampsia. The corresponding findings by I-Hsien Tsai MS et al, a gestational weight gain of >18kg increases the risk of preeclampsia [28].

The mechanism that higher body weight before pregnancy is associated with risk of preeclampsia is not clear. However adipose tissues from overweight and obese women thought to secrets inflammatory substances which can lead to chronic inflammatory and hence affects vascular activities. The etiology of preeclampsia remains unclear, though it has been reported to be a disease of endothelia dysfunction in which the cause of endothelial dysfunction is unknown [29]. The following factors have been mentioned to contribute to its mechanisms, obesity associated with inflammatory responses, immunological maladaptation, genetic components, and maternal intravascular inflammatory response to pregnancy [4, 29]

The strength of our current study was that it used data from the hospital-based cohort (hospital registry). Data stored in this registry have been reported to demonstrate both high validity and quality, confirming that hospital registries are a valuable resource in studying maternal and obstetric health outcomes, therefore identification of preeclampsia is shown to be accurate in such databases. Missing values for some variables and loss to follow up in the record linkage can affect our results. Most variables with missing values accounts for less than 1% and were not included in the multivariate analysis. Limited cases from sample size may lead to selection and misclassification bias, since we excluded all women who have preeclampsia in the first pregnancy and prepregnancy weight and height data used in this study were collected during ANC visit before the women develop preeclampsia, thus if small number of preeclampsia were misclassified so that bias would be differential misclassification. We also acknowledge the use of self-reported maternal prepregnancy weight as a limitation; it is possible that the calculated BMI may have been underestimated. However this have previously shown to be reliable for clinical researches. Unmeasured factors such as nutritional diet before and during pregnancy may lead to residual confounders and thus affect our study findings. The relatively small number of cases of preeclampsia led to wide confidence intervals for some BMI values. To our knowledge, these findings cannot be generalizable to all hospitals in Tanzania, rather to the similar hospital as KCMC and KCMC itself. We did not study the effect of prepregnancy BMI in association with neonatal outcome which could have given us a more comprehensive picture. Future studies with larger samples of overweight and obese women should be carried out to more accurately assess the association of prepregnancy BMI and risk of preeclampsia in the second pregnancy.

Conclusion

These findings add to the knowledge that prepregnancy BMI is associated with increased risk of preeclampsia. Overweight, obesity, weight loss between pregnancies, old age, and first pregnancy were associated with higher likelihood of preeclampsia. Similarly chronic hypertension and gestational hypertension were also associated with increased risk of preeclampsia. This calls for clinicians to counsel pregnant women on the consequences associated with high prepregnancy weight.

Contributors to authorship

Concept and design: D E M, A K D, T O, R T L and M J M. Analysis and interpretation of the data: D E M. Writing of the manuscript: D E M, A K D, T O, R T L. Final approval of the manuscript to be published: D E M, A K D, T O, R T L and M J M

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Author Disclosures

We declare that we have no competing interests.

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8.0 Figures, tables and appendices

Figure 1: Map of the study area

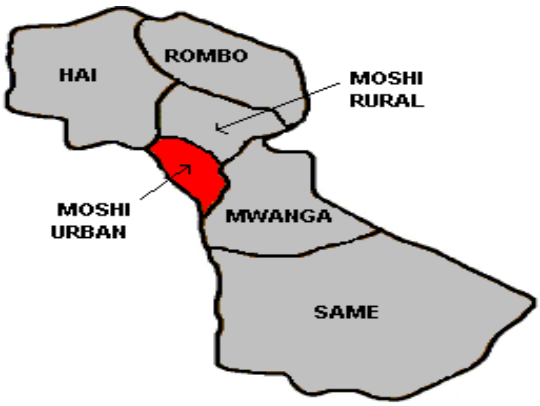

Figure 2: Population flow diagram (analysis of gravida 1 and 2 women, aims 1-3)

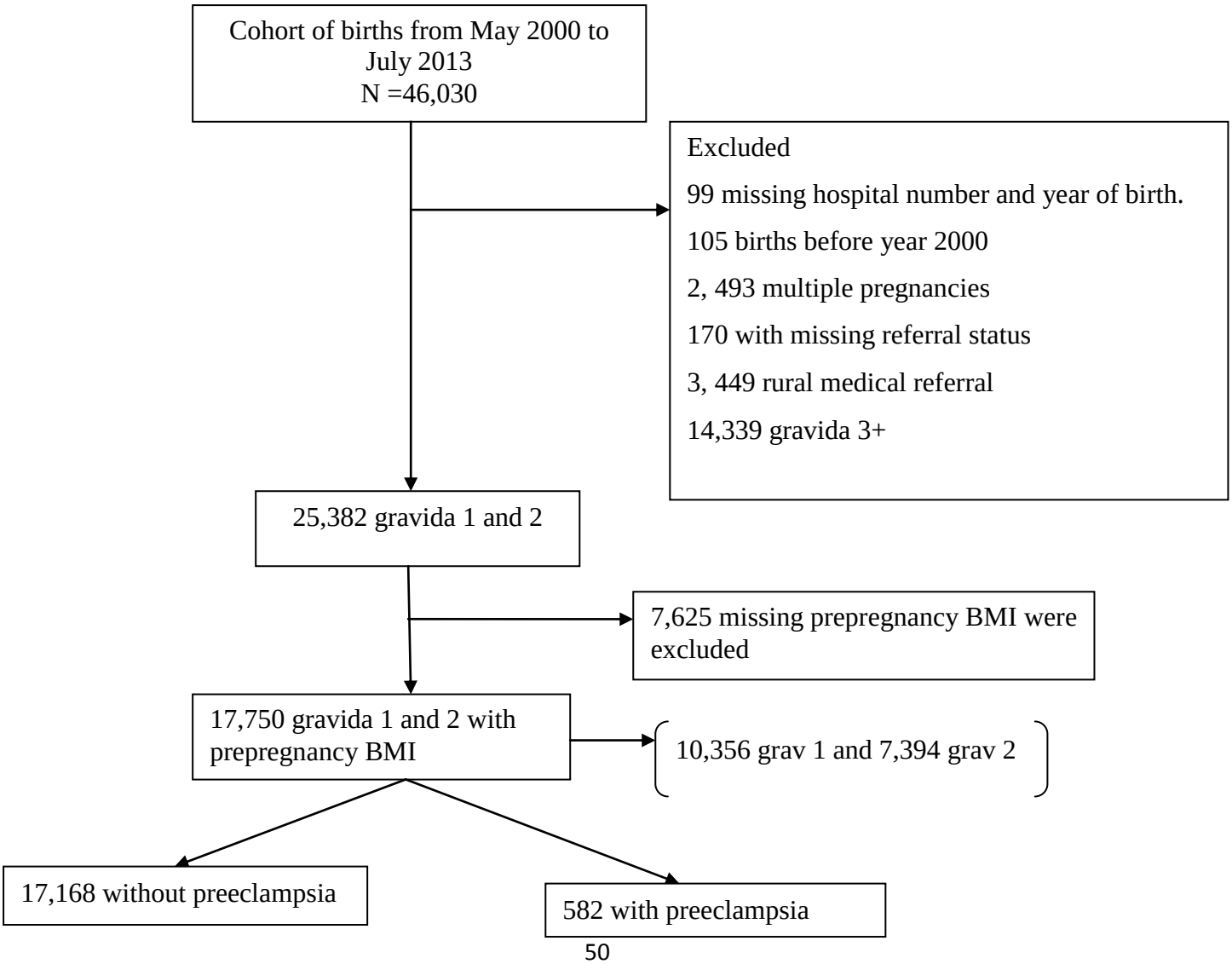

Figure 3: Population flow diagram (analysis of women with at least two recorded singleton pregnancies; aim 4)

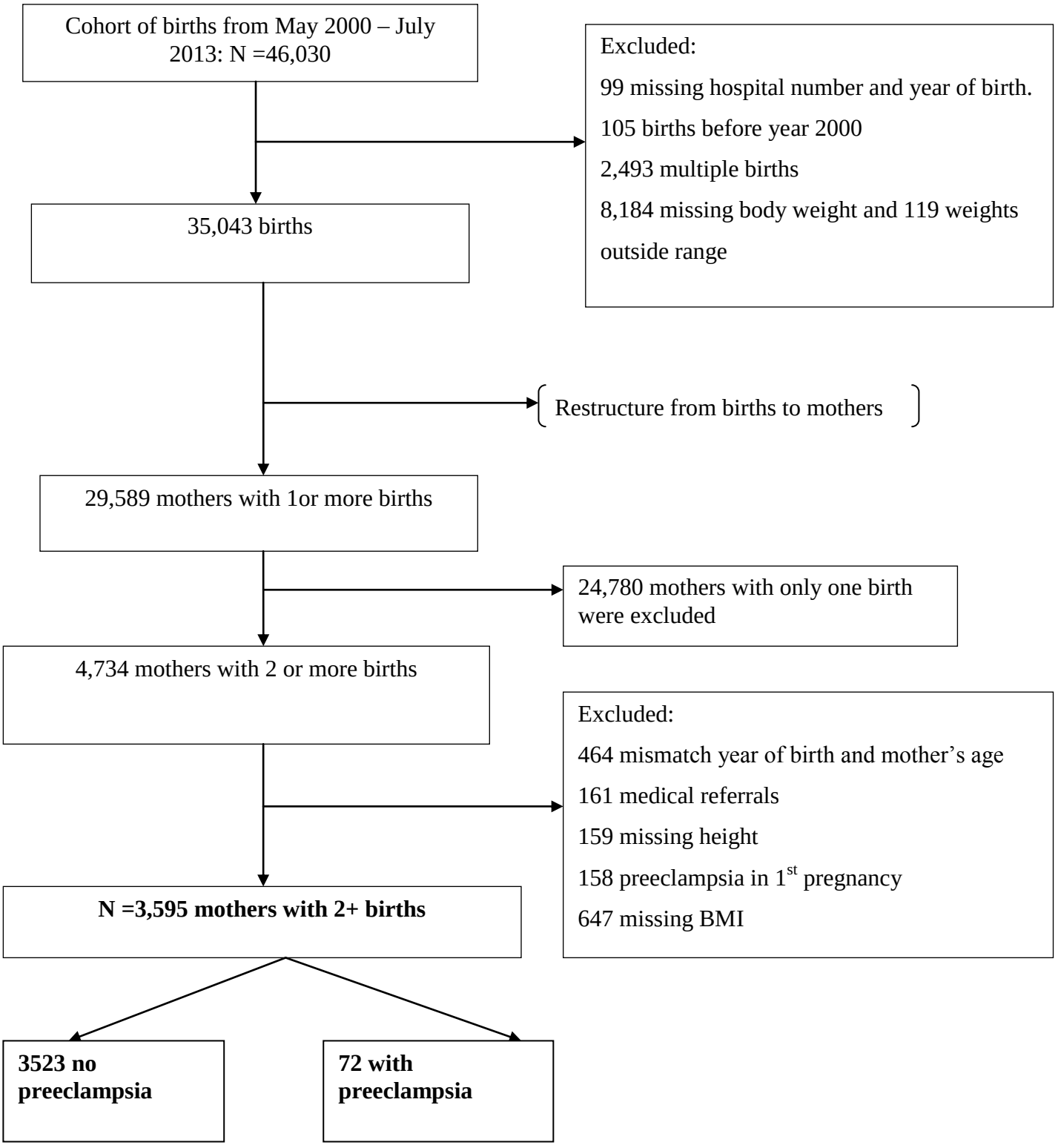

Table 1: Overview of birth record (aims 1-3) and record linkage analysis (aim 4).

Aims	Independent variables	Population	Dependent variable
Aims 1-3	**Main exposure:** Prepregnancy BMI **Covariates:** Social demographic variables from first and second pregnancy. Maternal characteristics from first and second pregnancy. **Mediators:** Chronic hypertension and heart diseases or diabetes before pregnancy.	gravida 1 gravida 2	Preeclampsia
Aim 4	**Main exposures:** Change in prepregnancy BMI/weight from 1st recorded to 2nd recorded pregnancy **Covariates:** Maternal characteristics in second pregnancy	1st recorded pregnancy 2nd recorded pregnancy	Preeclampsia in the second recorded pregnancy

Table 2a: Sociodemographic characteristics of the participants in relation to BMI (main exposure) (N=17,750). KCMC Medical birth registry July 2000-May 2013

Mothers characteristics	n	Mean BMI	BMI < 18.5 Underweight	BMI 18.5-24.9 Normal	BMI 25.0-29.9 Overweight	BMI > 30 Obese	Pearson $\chi 2$ p-value
Overall (n)	**17,750**		**1623**	**10563**	**4258**	**1306**	
%		**23.5**	**9.1%**	**59.5%**	**24%**	**7.4%**	
Mothers age (yrs)							<0.001
13-19	2151	21.8	16.7%	68.0%	13.5%	1.8%	
20-24	6440	22.8	10.6%	65.6%	19.4%	4.3%	
25-29	5757	24.0	7.5%	55.8%	27.7%	8.9%	
30-34	2611	25.0	4.5%	49.5%	32.9%	13.1%	
35-50	757	25.6	3.7%	45.6%	33.7%	17.0%	
Missing	34	23.9	2.9%	64.7%	23.5%	8.8%	
P for trend						**<0.001**	
Mothers education							<0.001
None	177	22.8	12.4%	66.1%	18.1%	3.4%	
Primary	9124	23.2	9.6%	62.9%	21.4%	6.1%	
Secondary (8-11 yrs)	1143	23.2	13.1%	57.0%	23.1%	6.7%	
Higher (12+ yrs)	7280	24.0	7.8%	55.4%	27.6%	9.2%	
Missing	26	22.2	15.4%	69.2%	15.4%	0.0%	
P for trend						**0.022**	
Marital status							<0.001
With partner	14816	23.6	8.6%	59.4%	24.6%	7.4%	
Without partner	2869	23.2	12.1%	60.1%	20.6%	7.1%	
Missing	65	24.3	6.2%	56.9%	24.6%	12.3%	
Mothers occupation							<0.001
Housewife	3568	23.0	10.9%	63.3%	20.8%	5.1%	
Farmer	2786	22.5	11.8%	67.2%	17.3%	3.6%	
Service	1286	23.8	7.3%	57.8%	27.4%	7.5%	
Business	4131	24.3	7.4%	54.6%	27.2%	10.8%	
Professional	3791	24.2	6.6%	54.7%	29.1%	9.6%	
Student	592	22.4	16.2%	61.1%	17.9%	4.7%	
Missing	1596	23.1	10.2%	62.7%	21.9%	5.3%	
Mothers tribe							<0.001
Chagga	10174	23.8	7.5%	58.1%	26.1%	8.3%	
Pare	2045	23.5	9.7%	59.8%	23.6%	6.9%	
Other	5531	23.0	12.0%	62.1%	20.2%	5.7%	
Ante natal care							<0.001
<4	8750	23.4	10.1%	60.5%	22.3%	7.1%	
≥4	8787	23.7	8.1%	58.5%	25.7%	7.7%	
Missing	213	23.1	11.7%	58.7%	24.9%	4.7%	
Mother's height							<0.001
≤155cm	4147	23.5	8.5%	61.2%	23.5%	6.7%	
155cm-164	8938	23.6	8.3%	60.7%	23.1%	7.9%	
≥165	4665	23.4	11.3%	55.7%	26.0%	6.9%	
P for trend						**0.007**	

Table 2b: **Maternal health related characteristics in relation to BMI (main exposure) among 17,750 singleton deliveries. KCMC Medical birth registry July 2000 - May 2013**

Maternal health characteristics	n	Mean BMI	BMI < 18.5 Underweight	BMI 18.5-24.9 Normal	BMI 25.0-29.9 Overweight	BMI > 30 Obese	Pearson $\chi 2$ p-value
Overall (n)	**17750**		**1623**	**10563**	**4258**	**1306**	
%		**23.5**	**9.1%**	**59.5%**	**24%**	**7.4%**	
Gravidity							<0.001
First	10356	22.9	11.2%	63.3%	20.5%	5.0%	
Second	7394	24.4	6.3%	54.1%	28.9%	10.6%	
Chronic Hypertension							<0.001
Yes	76	25.5	6.6%	39.5%	35.5%	18.4%	
No	17674	23.5	9.2%	59.6%	23.9%	7.3%	
Gestational hypertension							0.033
Yes	41	25.0	2.4%	46.3%	41.5%	9.8%	
No	17709	23.5	9.2%	59.5%	23.9%	7.4%	
Diabetes before							0.167
Yes	21	24.9	9.5%	42.9%	28.6%	19.0%	
No	17729	23.5	9.1%	59.5%	24.0%	7.3%	
Heart diseases before							0.007
Yes	53	22.5	22.6%	47.2%	22.6%	7.5%	
No	17697	23.5	9.1%	59.5%	24.0%	7.4%	
Gestational age							<0.001
Below 37	2634	23.2	11.6%	60.8%	20.7%	6.9%	
More than 37	13683	23.6	8.5%	59.4%	24.7%	7.4%	
Missing	1433	23.4	11.1%	58.1%	23.2%	7.5%	

Table 3: Relationship between risk factors and preeclampsia among singleton deliveries at KCMC Medical birth registry July 2000 – May 2013

Maternal health characteristics	No preeclampsia (n)	Pre-eclampsia [n (%)]	$\chi 2$	Crude OR and 95% CI	P-value	Adjusted OR and 95% CI	P-value
Mother's BMI			**<0.001**				
<18.5 underweight	1583	40 (2.5%)		0.9 (0.6-1.2)	0.4	0.8 (0.6-1.1)	0.206
18.5-24.9 normal	10264	299(2.8%)		Ref	Ref	Ref	Ref
25.0-29.9 overweight	4077	181 (4.3%)		1.5 (1.3-1.8)	<.001	1.5 (1.2-1.7)	0. 001
30 thru highest obese	1244	62 (4.7%)		1.7 (1.3-2.3)	<.001	1.7 (1.2-2.1)	<0.001
P for trend		**< 0.001**		**<0.001**		**<0.001**	
Mother's age			**<0.001**				
13-19	2090	61(2.8%)		1 (0.8 - 1.5)	0.59	1 (0.7-1.4)	0.996
20-24	6270	169 (2.6%)		Ref	Ref	Ref	Ref
25-29	5570	187 (3.2%)		1.3 (1.0-1.5)	0.041	1.1 (0.9-1.4)	0.279
30-34	2497	114 (4.4%)		1.7 (1.3-2.2)	<.001	1.5 (1.1-1.9)	0.006
35-50	708	49(6.5%)		2.6 (1.9-3.6)	<.001	2.3 (1.6-3.2)	<0.001
P for trend		**< 0.001**		**<0.001**		**<0.001**	
Mother's education			**0.082**				
None	172	5 (2.8%)		0.8(0.3-1.9)	0.55	1.2 (0.5-2.9)	0.744
Primary	8847	277 (3.0%)		0.8 (0.7-1.0)	0.022	1.1 (0.9-1.4)	0.401
Secondary (8-11)	1112	31 (2.7%)		0.7 (0.5-1.0)	0.101	0.8 (0.5-1.3)	0.338
Higher (12+)	7012	268 (3.7%)		Ref	Ref	Ref	Ref
P for trend		**0.022**		**0.022**		**0.678**	
Marital status			**0.002**				
With partner	14357	459 (3.1%)		0.7 (0.6-0.9)	0.003	0.7 (0.6-0.9)	0.003
Without partner	2749	120 (4.2%)		Ref	ref		
Mother's occupation			**< 0.001**				
Housewife	3464	104 (2.9%)		1 (0.8-1.4)	0.91	1 (0.7-1.4)	0.881
Farmer	2706	80 (2.9%)		Ref	Ref	Ref	Ref
Service	1227	59 (4.6%)		1.6 (1.1-2.3)	0.005	1.4 (1.0-2.0)	0.054
Business	4018	113 (2.7%)		0.9 (0.7-1.3)	0.736	0.8 (0.6-1.2)	0.306
Professional	3630	161 (4.2%)		1.5 (1.1-2.0)	0.004	1.3 (0.9-1.8)	0.181
Student	573	19 (3.2%)		1.1(0.7-1.9)	0.658	1.1 (0.6-1.9)	0.727
Mother's tribe			**<0.001**				
Chagga	9884	290 (2.9%)		Ref	Ref	Ref	Ref
Pare	1952	93(4.5%)		1.6 (1.3-2.1)	<0.001	1.9 (1.4-2.4)	<0.001
Others	5332	199 (3.6%)		1.3 (1.0-1.5)	0.01	1.4 (1.2-1.8)	<0.001
Mother's height			**0.005**				
<155 cm	4022	125 (3.0%)		0.7 (0.6-0.9)	0.012	0.7 (0.6-1.0)	0.023
155-164 cm	8668	270 (3.0%)		0.7 (0.6-0.9)	0.002	0.7 (0.6-0.9)	0.003
≥165	4478	187 (4.0%)		Ref	Ref	Ref	Ref
P for trend		**0.007**		**0.007**		**0.069**	

*All variables are in the multivariable model.

Table 4: Sociodemographic characteristics in the second recorded pregnancy in relation to preeclampsia among 3595 women (objective 4, record linkage analysis). KCMC Medical birth registry July 2000 – May 2013

Maternal characteristics	**Number of births**	**Preeclampsia n (%)**	**χ2**	**Unadjusted OR**	**P value**	**Adjusted OR***	**P value**
Overall	**3595**	**72 (2.0%)**					
Maternal age (y)			**0.88**				
Less than 25	707	15 (2.1)		1.1	0.72	1.3	0.5
25-34	2150	41 (1.9)		ref		ref	
35 or more	738	16 (2.2)		1.1	0.66	1.0	0.9
P for trend		**0.94**					
Maternal education			**0. 24**				
Less than 12	1912	32 (1.7 %)		0. 7	0. 1	0. 7	0. 18
12	183	3 (1.6 %)		0. 7	0. 4	0. 7	0. 54
13	1497	37 (2.5 %)		ref		ref	
P for trend		**0. 10**					
Marital status			**0. 91**				
Married	3474	70 (2.0 %)		ref		ref	
Unmarried	107	2 (1.9 %)		0. 9	0. 9	1.0	0. 95
ANC visits			**0. 24**				
Less than 4	2257	39 (1.7 %)		ref		ref	
Equal or more than 4	1311	30 (2.3 %)		1.3	0. 2	1.3	0. 32
BMI			**0. 024**				
Less than 18.5	79	3 (3.8 %)		2.7	0. 11	2.7	0. 11
18.5-24.9	1571	23 (1.5 %)		ref		ref	
25.0-29.9	1279	24 (1.9 %)		1.3	0. 39	1.2	0.54
30 or more	666	22 (3.3 %)		2.3	0. 006	2.0	0.002
P for trend		**0. 03**					

*Adjusted for maternal age, education, prenatal care, marital status and BMI2

Table 5: Association between changes in BMI between pregnancies and risk of preeclampsia in the second recorded pregnancy among 3, 595 women (objective 4, record linkage analysis). KCMC Medical birth registry July 2000 – May 2013.

First pregnancy	Second pregnancy	Total births	Preeclampsia (%)	Crude OR and (95%CI)	P value	Adjusted OR* and 95%CI	P value
Underweight	Underweight	36	0				
Underweight	Normal	90	0				
Underweight	Overweight	19	0				
Underweight	Obese	1	0				
Normal	Underweight	37	3 (8.1 %)	5.8 (1.6 -20.4)	0.006	6.0 (1.7-21.5)	0.005
Normal	Normal	1334	20 (1.5 %)	Ref		Ref	
Normal	Overweight	629	13 (2.1 %)	1.4 (0.7-2.8)	0.363	1.2 (0.6-2.5)	0.58
Normal	Obese	120	2 (1.7 %)	1.1 (0.3 – 4.8)	0.89	1.1 (0.2-4.8)	0.90
Overweight	Underweight	4	0				
Overweight	Normal	134	2 (1.5 %)	1.0 (0.2 – 4.3)	0.99	1.0 (0.2-4.5)	0.97
Overweight	Overweight	578	9 (1.6 %)	1.0 (0.5-2.3)	0.92	1.0 (0.5-2.3)	0.96
Overweight	Obese	298	12 (4.0 %)	2.8 (1.3-5.7)	0.006	2.2 (1.0-4.9)	0.046
Obese	Underweight	2	0				
Obese	Normal	13	1 (7.7 %)	5.5 (0.7 – 44.1)	0.11	5.6 (0.7-45.9)	0.11
Obese	Overweight	53	2 (3.8 %)	2.6 (0.6-11.3)	0.21	2.8 (0.6-12.1)	0.18
Obese	Obese	247	8 (3.2 %)	2.2 (1.0 -5.0)	0.063	2.2 (0.9-5.0)	0.073

*Adjusted for maternal age, education, prenatal care, marital status and BMI2

Table 6: Weight change between pregnancies among 3595 women (objective 4, record linkage analysis). KCMC Medical birth registry July 2000 – May 2013

Weight change between pregnancies	Total births	Mean weight in last pregnancy	Preecla N, %	Unadjusted OR and 95 % CI	P value	Adjusted OR and 95 % CI	P value
Lost weight							
-20 to -29kg	18	58.5	1 (5.6 %)	3.2 (0. 4-24.9)	0. 27	3.8 (0. 5-30)	0. 2
-19 to -10kg	119	57.7	5 (4.2 %)	2.4 (0. 9-6.3)	0. 08	2.5 (0. 9 – 6.9)	0. 06
-9 to -5kg	240	59.1	3 (1.2 %)	0. 7 (0. 2-2.3)	0. 54	0. 8 (0. 2-2.5)	0. 7
P for trend				**0.12**		**0.053**	
-4 to 4kg	1554	62.5	28 (1.8 %)	ref		ref	
Gained weight							
5 – 9kg	736	68.4	11 (1.5 %)	0. 8 (0. 4-1.7)	0. 59	0. 8 (0. 4-1.6)	0. 5
10 – 19kg	740	74.5	17 (2.3 %)	1.3 (0. 6-2.4)	0. 42	0. 9 (0. 5-1.9)	0. 8
20 – 29kg	165	82.8	6 (3.6 %)	2.1 (0. 8-5.0)	0. 11	1.6 (0. 6-4.2)	0. 4
P for trend				**0.16**		**0.97**	

Adjusted for maternal age, mothers education, marital status, perinatal care, and BMI 2

Table 7: Prepregnancy BMI in second pregnancy and effect on preeclampsia among 3,595 women (objective 4, record linkage analysis), Logistic regression in three steps. KCMC Medical birth registry July 2000 – May 2013.

		*BMI			BMI & **COVARIATES			BMI, COVARIATES AND WEIGHT CHANGE		
BMI categories	**Preecla (N)**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Underweight	3(3.8 %)	2.7	0.8 -9.0	0.11	2.7	0.8 – 9.1	0.1	2.2	0.6 – 7.8	0.2
Normal	23(1.5 %)	ref	ref		ref	ref		ref	ref	
Overweight	24(1.9 %)	1.3	0.7 – 2.3	0.39	1.2	0.7 – 2.2	0.5	1.2	0.6 – 2.3	0.5
Obese	22 (3.3 %)	2.3	1.3 – 4.2	0.006	2.0	1.1 – 3.8	0.024	2.0	0.9 – 4.1	0.07

*Main exposure: Prepregnancy BMI

**Covariates: Maternal age, mother's education, prenatal care and marital status

Appendix 1: questionnaire

KCMC Medical Birth Registry

Version 5 - November 2004

1 Basic information concerning mother

1.1 Mothers date of birth: ____ **Age:** ____ **1. Mothers name:** ____

1.4 Hospital number: ____ **1. Address:** ____

1.6 Birth number: ____ **1. Date of interview:** ____

1.8 Date of admission: ____ **1. Interview by:** ____

Referred for delivery: ☐1 Yes ☐2 No (*self referral*) If yes: **Referred from:** ☐1 Home ☐2 Regional hospital ☐3 District hospital ☐4 Other, specify: ____

Referred during ☐1 Admitted in labour ☐2 Admitted before

Reason for referral: ____

1.9 Official date of discharge: ____ **1.10 Date leaving hospital:** ____

1.1 Current residence: ☐1 Rural ☐2 Urban ☐3 Semi urban

Area of mother's residence: ____

1.12 Mothers childhood residence: ☐1 Rural ☐2 Urban ☐3 Semi urban

Area of mother's childhood residence: ____

1.1 Highest educational ☐1 None ☐2 Primary (1-7) ☐3 Secondary (8- ☐4 Higher (12+)

1.1 Current ☐1 Housewife ☐2 Farmer ☐3 Service ☐4 Business ☐5 Professional ☐6 Student ☐7 Others ____

1.1 Current marital ☐1 Married Age at first ____ ☐2 Single ☐3 Widowed ☐4 Remarried ☐5 Divorced ☐6 Polygamous Add wife number: ____

No of previous pregnancies ____

1.1 Regular menstrual periods: ☐1 Yes ☐2 No Age at menarch ____

1.17 Genital mutilation *(Circumcision)* ☐1 Yes ☐2 No **If yes, at** ____ **If yes, type:** ☐1 Type one ☐2 Type two ☐3 Type three

1.1 Mother's tribe: ☐0 Chagga ☐0 Pare ☐0 Masai ☐ Other ____

1.19 Religion: ☐1 Catholic ☐2 Protestant ☐3 Muslim ☐4 Others ____ ☐4 Other types ____

2 Questions concerning the father of the child:

2.1 Father's name: ____ **2.2 Father's age:** ____

2.3 Current occupation of father: **2.4 Father's** ☐1 None

☐0 Farmer
☐0 Business
☐0 Skilled worker
☐0 Unskilled worker
☐0 Service
☐06 Official
☐07 Professional
☐08 Student
☐09 Unemployed
☐10 Other ⇓

educational level:
☐2 Primary (1-7)
☐3 Secondary (8-11)
☐4 Higher (12+)

2.5 Father's tribe:
☐1 Chagga
☐2 Pare
☐3 Masai
☐4 Others ➲

3 Questions concerning home conditions:

3.1 Source of drinking
☐1 Tap water
☐2 Well
☐3 River
☐4 Spring
☐5 Other, specify

3.2 Boiling of drinking
☐1 Yes
☐2 No

3.3 Distance to water, if not tap:
☐1 Less than 1 km (less ½ hour
☐2 More than 1 km, specify in km:

3.4 Home toilet:
☐1 Pit latrine
☐2 Flush
☐3 Others ➲

4 Mothers health before and during present pregnancy

4.1 Body weight (kg): (before pregnancy) ☐☐☐

4. Body height (cm): ☐☐☐

4. Blood transfusio ☐1 Yes ☐2 No

4.4 Serious diseases

☐0 Diabetes
☐0 Hypertension
☐0 Heart diseases
☐0 Epilepsy
☐0 Malaria
☐0 Anaemia
☐0 Gynaecological
☐0 Liver disease
☐0 Kidney disease
☐1 Lung disease
☐1 Tuberculosis
☐1 Sickle cell
☐1 Other, specify ⇓

4.5 Have you ever practised family
☐1 Yes
☐2 No

Months trying to get pregnant: ☐☐☐

If yes, what kind of prevention
☐0 Pills
☐0 Injections
☐0 IUD
☐0 Condoms
☐0 Implant
☐0 Lactation
☐0 Withdrawal
☐0 Natural
☐0 Abstinence
☐1 Traditional
☐1 Other specify ⇓
☐☐

4.6 Antenatal care in this pregnancy:
☐1 Yes
☐2 No

If yes: First medical appointment ☐☐☐☐☐☐

Number of ☐☐

If date unknown, estimate first
☐1 0-12. week of gestation
☐2 13-20. week
☐3 21-30. week
☐4 After 31. week

4.7 L.M.P: ☐☐☐☐☐☐

4. Ultrasound
☐1 Yes
☐2 No

4.9 E.D.D. based on clinical estimate: ☐☐☐☐☐☐

4.1 Do you
☐1 Yes
☐2 No

If yes: how many cigarettes per day:

Smoking during this pregnancy:
☐1 Yes
☐2 No

Chewing
☐1 Yes
☐2 No

Chewing tobacco during this pregnancy:
☐1 Yes
☐2 No

4.1 Do you drink alcoholic
☐1 Yes
☐2 No

If yes:
☐1 Every day
☐2 More than once a week
☐3 Once a week
☐4 Occasionally

Did you also drink alcoholic beverages during this

If yes:
☐1 Every day
☐2 More than once a week
☐3 Once a week
☐4 Occasionally

4.1 Drugs on regular basis?
☐1 Yes ❶
☐2 No

If yes:
☐1 Modern
☐2 Traditional

Did you take any drugs during this pregnancy:
☐1 Yes ❶
☐2 No

If yes, specify:
☐1 Modern
☐2 Traditional

Did you take any drugs at time of
☐1 Yes ❶
☐2 No

Drugs for infertility:
☐1 Yes
☐2 No

4.1 Blood group (AB0) ☐

Rh: ☐ Anti-D in previous
☐1 Yes
☐2 No
☐3 Unknown

VDRL
☐1 Positive
☐2 Negative
☐3 Unknown

Hb ☐☐☐

Hb measurement done:
☐1 On Admission
☐2 Last visit to ANC

HIV test
☐1 Yes
☐2 No

If yes, result:
☐1 Negative
☐2 Positive

Treatment during this pregnancy:
☐1 Yes
☐2 No

Specify

4.1 Diseases and complications during present pregnancy.

☐ 1 Yes (specify below)
☐ 2 No

☐ 0 Gestational diabetes
☐ 0 Diabetes
☐ 0 Hypertension
☐ 2 Preeclampsia, mild
☐ 2 Preeclampsia, severe
☐ 0 Eclampsia

☐ 0 Epilepsy
☐ 0 Bleeding
☐ 0 Anaemia
☐ 0 Hyperemesis
☐ 1 Malaria
☐ 1 Jaundice
☐ 1 Schistosomiasis

☐ 1 Gynaecological disease
☐ 1 Tromboembolic disease
☐ 1 Heart disease
☐ 1 Tuberculosis
☐ 1 Lung disease
☐ 1 Infections, specify
☐ 1 Others, specify

5 Questions concerning the delivery

5.1 At birth ☐ 1 Single birth ☐ 2 Multiple birth — If multiple, add no. of children: ☐ — **Weight on admission:** ☐☐☐☐

5.2 Complications during delivery
☐ 1 PROM
☐ 2 Bleeding > 500 ml
☐ 3 3-4. degree tear
☐ 4 Abruption of placenta
☐ 5 Placenta previa
☐ 6 Other complications

5.3 Induction of labour ☐ 1 Yes ☐ 2 No — If yes: ☐ 1 Amniotomy ☐ 2 Oxytocin ☐ 3 Prostaglandin

5.4 Others ☐ 1 Episiotomy ☐ 2 Symphysiotomy

5.5 Analgesia: ☐ 1 Yes ☐ 2 No

5.6 Anaesthesia: ☐ 1 General ☐ 2 Spinal/Epidural

5.8 Blood Loss (ml) ☐☐☐☐

Specify type other type of complication

5.7 Gestational age at birth clinical estimate ☐☐

5.9 Mother's health after delivery ☐ 1 Good ☐ 2 Fair ☐ 3 Bad ☐ 4 **Maternal death**

Cause of death:

Post mortem: ☐ 1 Yes ☐ 2 No

6 Status of 1. child (Always fill inn)

6.1 Date of delivery ☐☐.☐☐.☐☐☐☐

6.2 Time of delivery ☐☐:☐☐

6.3 Sex ☐ 1 Male ☐ 2 Female ☐ 3 Unknown, unspec.

6.4 Birth weight (gram) ☐☐☐☐

6.5 Length (cm) ☐☐

6.6 Head circum ☐☐

6.7 Presentation: ☐ 1 Cephalic ☐ 2 Breech ☐ 3 Transverse ☐ 4 Other

6.8 Status ☐ 1 Live born ☐ 2 Live born transferred to paediatrics dept ☐ 3 Stillborn ☐ 4 Neonatal death

Cause of death

6.9 If stillborn: ☐ 1 Dead before labour ☐ 2 Dead during labour ☐ 3 Unknown, unspec.

If stillborn, also specify: ☐ 1 Dead before admission ☐ 2 Dead after admission

And: ☐ 1 Fresh ☐ 2 Macerated

Post mortem: ☐ 1 Yes ☐ 2 No

6.10 Apgar score: 1min ☐☐ 5 min ☐☐ 10 min ☐☐

If neonatal death: ☐ 1 Died within first 24 hours ☐ 2 Died within first week

Date of death: ☐☐.☐☐.☐☐☐☐

6.11 Mode of delivery: ☐ 1 Spontaneous ☐ 2 Vacuum, vaginal ☐ 3 Forceps, vaginal ☐ 4 CS elective ☐ 5 CS others ☐ 6 Assisted breech ☐ 7 Destructive operative

Indication when caesarean section: Primary / Secondary

6.12 Failed intervention ☐ 1 Vacuum ☐ 2 Forceps

6.13 Does the child have any of these conditions? ☐ 1 Birth defects ☐ 2 Injuries ☐ 3 Diseases ☐ 4 HIV Positive

Status on 2. child (For multiple births – not for singletons, if more than twins add extra copy of this page)

6.1 Date of delivery ☐☐.☐☐.☐☐☐☐

6.2 Time of delivery ☐☐:☐☐

6.3 Sex ☐ 1 Male ☐ 2 Female ☐ 3 Unknown, unspec.

6.4 Birth weight (gram) ☐☐☐☐

6.5 Length ☐☐

6.6 Head ☐☐

(cm) **Circum**

6.7 Presentation:
- ☐ 1 Cephalic
- ☐ 2 Breech
- ☐ 3 Transverse
- ☐ 4 Other

6.8 Status
- ☐ 1 Live born
- ☐ 2 Live born transferred to paediatrics dept
- ☐ 3 Stillborn
- ☐ 4 Neonatal death

Cause of death

6.9 If stillborn:
- ☐ 1 Dead before labour
- ☐ 2 Dead during labour
- ☐ 3 Unknown, unspec.

If stillborn, also specify:
- ☐ 1 Dead before admission
- ☐ 2 Dead after admission

And:
- ☐ 1 Fresh
- ☐ 2 Macerated

Post mortem:
- ☐ 1 Yes
- ☐ 2 No

6.10 Apgar score: **1min** **5 min** **10 min**

If neonatal death:
- ☐ 1 Died within first 24 hours
- ☐ 2 Died within first week

Date of death:

6.11 Mode of delivery:
- ☐ 1 Spontaneous
- ☐ 2 Vacuum, vaginal
- ☐ 3 Forceps, vaginal
- ☐ 4 CS elective
- ☐ 5 CS others
- ☐ 6 Assisted breech
- ☐ 7 Destructive operative

Indication when caesarean section:
Primary
Secondary

6.12 Failed intervention
- ☐ 1 Vacuum
- ☐ 2 Forceps

6.13 Does the child have any of these conditions?
- ☐ 1 Birth defects
- ☐ 2 Injuries
- ☐ 3 Diseases
- ☐ 4 HIV Positive

Appendix 2: Ethical approval from Kilimanjaro Christian Medical University College research ethics committee

CRERC FORM 07

TUMAINI UNIVERSITY MAKUMIRA

KILIMANJARO CHRISTIAN MEDICAL UNIVERSITY COLLEGE
P. O. Box 2240, MOSHI, Tanzania

RESEARCH ETHICAL CLEARANCE CERTIFICATE

No 641

Research Proposal No. 633

Study Title: EFFECT OF PRE-PREGNACY BODY MASS INDEX AND CHANGES IN PRE-PREGNACY BODY MASS INDEX ON RISK OF PRE-ECLAMPSIA/ECLAMPSIA IN NORTHERN TANZANIA: A REGISTRY BASED STUDY

Study Area: KCMC

P. I Name: DORAH MREMA

Institution (s): KILIMANJARO CHRISTIAN MEDICAL UNIVERSITY COLLEGE

The Proposal was approved by CRERC on: 12TH SEPTEMBER,2013

Duration of Study: FROM: 12TH SEPTEMBER,2013 TO 12TH SEPTEMBER,2014

Name: BEATRICE Z. TEMBA
Signature.....
Research Administrator – CRERC

Name : PROF.FRANKLIN MOSHA
Signature.....
Chairman – CRERC

Appendix 3: Ethical approval from Tanzania national institute for medical research (NIMR) 2003

THE UNITED REPUBLIC OF TANZANIA

National Institute for Medical Research
P.O. Box 9653
Dar es Salaam
Tel: 255 22 2130770/2135185
Fax: 255 22 2130060/2131864
E-mail: headquarters@nimr.or.tz

Ministry of Health
P.O. Box 9083
Dar es Salaam
Tel: 255 22 2120362-7
Fax: 255 22 2110986

NIMR/HQ/R.8a/Vol. IX/126

5th May, 2003

Prof J Mlay,
KCMC,
P o Box 3010,
Moshi, Tanzania

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: "Registry based reproductive health research: Medical Birth registration at KCMC" Mlay J et al, Principal Investigator, has been granted clearance to be conducted in Tanzania. The PI of the study must ensure that the following conditions are fulfilled:

[√] Progress report is made available to MoH and NIMR every six months.
[√] Permission to publish the results is obtained from NIMR (manuscript being attached to the request) before any publication is made.
[√] Copies of final publications are made available to MoH and NIMR for action and records.

CHAIRMAN
NATIONAL MEDICAL RESEARCH COORDINATING COMMITTEE

This is to certify that Permission is hereby granted for the conduct of the study entitled: "Registry based reproductive health research: Medical Birth registration at KCMC" Mlay J et al Principal Investigator, within the health services and/or communities in Tanzania.

CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH

Appendix 4: Ethical approval from Regional Ethical Committee (Health Regional III) Norway 1999

Certified translation from Norwegian

UNIVERSITY OF BERGEN
Faculty of Medicine
Harald Härfagresgt. 1, N-5020
Phone: +47 55 58 20 84/86
Fax: +47 55 58 96 82
E-mail: Rek-3@uib.no

Regional committee for
medical research ethics
Health region II

Bergen, 7 September 1999
Journal no.: 334799-64.99

Professor Rolv Terje Lie
Section for medical statistics and data
Faculty of Medicine, University of Bergen
N-5021 BERGEN

Dear Sir,

Re Project: Medical Birth Registry at Kilimanjaro Christian Medical Centre (KCMC), Tumaini University, Moshi, Tanzania
Strategic concentration for research and education oriented towards developing countries – part of the Ministry of Foreign Affairs' strategy for support for developing countries, 1999 (64.99)

We refer to your application for an ethical assessment dated 7 July 1999.

The Committee considered the matter at its meeting on 26 August 1999.

The establishment of a birth registry is in itself not a research project and it is therefore not within our remit to perform an ethical assessment of the matter.
To comment on the application, however, we do not see any ethical problems in establishing such a registry provided the necessary information is collected on the basis of informed consent and the data is stored securely so that unauthorised persons are unable to gain access

UNIVERSITTET I BERGEN
Det medisinske fakultet
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Regional komitè for
medisinsk forskningsetikk
Helseregion III

Bergen, 07.09.99
Jnr.: 334799-64.99

Professor Rolv Terje Lie
Seksjon for medisinsk statistikk og data
Det medisinske fakultet, UiB
5021 BERGEN

Ad. Prosjekt: Medisinsk fødselsregister ved Kilimanjaro Chrisitan Medical Centre (KCMC), Tumaini University, Moshi, Tanzania.
Strategisk satsing for u-landsorientert forskning og utdanning - ledd i Utenriksdepartementets strategi for u-landsstøtte, 1999 (64.99)

Det vises til Deres søknad om etisk vurdering datert: 07.07.99.

Komiteen behandlet saken i sitt møte den 26.08.99.

Oppretting av et fødselsregister er ikke et forskningsprosjekt i seg selv og følgelig faller det utenfor vårt mandat å foreta en etisk vurdering av saken.
Som en kommentar vil vi allikevel si at vi ikke ser noen etiske problemer med å opprette et slikt register dersom innsamling av nødvendig informasjon skjer på grunnlag av det informerte samtykke og at dataene oppbevares forsvarlig slik at ikke uvedkommende får adgang til opplysninger i registeret. Den endelige tillatelse til å opprette fødselsregisteret må innhentes av landets egne myndigheter.

Vi ønsker dem lykke til med prosjektet.

Vi vil for øvrig gjøre Dem oppmerksom på at REK nå har tatt i bruk et nytt skjema for etisk vurdering, som vi ber Dem benytte ved eventuelle seinere prosjektsøknader. Opplysninger om dette finner De på vår side på verdensveven: http://www.etikkom.no/NEM/REK/rek.htm.

Vennlig hilsen

Olav Dahl
leder

Arne Salbu
sekretær

to the information therein. The final permission to establish a birth registry must be obtained from the country's own authorities.

We wish you the best of luck with your project.

Incidentally, we would point out that REK have now introduced a new form for ethical assessments, and we would ask you to use this in subsequent project applications. You will find information about this on the worldwide web:
http://www.etikkom.no/NEM/REK/rek.htm.

Yours faithfully,

(s.) Olav Dahl
Committee Chairman

(s.) Arne Salbu
Secretary

True translation certified:
Bergen, 26 March 2003

BRYGGEN TRANSLATØRBYRÅ A/S

STATSAUTORISERT TRANSLATØR
JO-ANN R. MIETLE
BERGEN
NORSK - ENGELSK - ENGELSK NORSK

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