Student's Journal of Health Research Africa
e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.3 No. 3 (2026): March 2022 Issue
https://doi.org/10.51168/sjhrafrica.v3i3.2622
Review Article

Fetal hypoxia and maternal obesity – A systematic review.

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Abstract

Background
This systematic review aims to evaluate the association between maternal obesity and fetal hypoxia and to synthesize existing evidence on the pathophysiological mechanisms linking these two conditions.

Materials and methods
Original research articles published between 2020 and 2024 were included. Eligibility criteria comprised case studies and scientific literature specifically addressing fetal hypoxia and maternal obesity, while irrelevant studies were excluded. Databases searched included PubMed, Lilacs, Embase, Scopus, and Web of Science (last search: April 2026). A total of 68 records were identified, of which 5 studies met the inclusion criteria. Data items extracted included first author, year, country, study type, and outcomes. Data synthesis was performed narratively following PRISMA guidelines. Study quality was assessed using the STROBE checklist.

Results
Following PRISMA guidelines, the five included studies consistently demonstrated that maternal obesity is associated with signs of chronic fetal hypoxia, altered placental phenotype, increased oxidative metabolism, and disruptions in maternal-placental-fetal immunology. Key findings include increased hypoxia-sensitive parameters in fetal blood, elevated inflammatory markers, and reduced placental vascular branching in obese pregnancies.

Conclusion
Maternal obesity is becoming more common, particularly in younger age groups, at a startling rate that has serious consequences for public health. In terms of morbidity and resources, the obesity epidemic is quite concerning. It has been calculated that the cost of obesity is five times higher than that of non-obese women.

Need for future research.
Future research should focus on identifying specific adipokine, insulin, and angiogenic factor combinations that lead to different neonatal phenotypes, as well as developing targeted interventions to prevent fetal hypoxia in obese pregnancies.

Keywords: Obesity; fetal hypoxia; pregnancy; placenta; gestational diabetes; inflammation
Submitted: January 10, 2022 Accepted: February 28, 2022 Published: March 30, 2022

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Introduction

One of the most frequent problems in prenatal life is hypoxia, or oxygen deprivation. Due to uterine contractions and/or compression of the umbilical cord, brief episodes of acute hypoxia, lasting a few minutes, are linked to labor and delivery. Chronic fetal hypoxia is the term used to describe oxygen deprivation of the fetus that lasts for several weeks or even months. Increased placental vascular resistance, which can arise from placental insufficiency, preeclampsia, or any inflammatory condition during pregnancy, including chorioamnionitis, gestational diabetes, or even maternal obesity, is the most prevalent effect of complex pregnancy. Gestational diabetes mellitus (GDM), which has a prevalence of 2% to 25% worldwide and varies by country, is a disorder that complicates pregnancies and is exacerbated by overweight and obesity. For both mother and child, GDM presents serious short-term and long-term health risks. Increased rates of prenatal hypertension, pre-eclampsia, and Caesarean section for the mother, as well as macrosomia and perinatal hypoglycemia for the fetus, are among the short-term dangers linked to GDM. Over time, women with a history of GDM are more likely to develop metabolic and vascular disorders, as are their children. The first line of treatment for GDM is diet and lifestyle modifications; if they are insufficient, treatment for hyperglycemia may be initiated.

For their biological processes, all aerobic organisms need oxygen. Oxidative phosphorylation (OXPHOS) in mitochondria uses over 90% of this oxygen to produce energy. Thus, hypoxia, or oxygen shortage, is a risk for which detection and rescue systems have been developed. Reduced oxygen availability at high altitudes is linked to higher newborn mortality and a 100 g/1000 m reduction in birth weight. The cellular hypoxia-response pathway is triggered by oxygen deficiency or hypoxia. Acute hypoxia increases breathing by activating carotid chemoreceptors and the sympathetic nervous system. However, a significant adaptation occurs at the transcriptional level and is controlled by the enzymes that function as cellular oxygen sensors, the hypoxia-inducible factor (HIF) and HIF prolyl 4-hydroxylases (HIF-P4Hs). The activation of erythropoiesis and angiogenesis through the overexpression of erythropoietin and vascular endothelial growth factor, respectively, and the change in energy metabolism to promote oxygen-independent glycolytic metabolism and reduce oxidative phosphorylation (OXPHOS) are two important adaptations. Additionally, HIF increases the expression of glucose transporters (GLUTs) and important glycolysis-related enzymes, including phosphofructokinase (PFK) and pyruvate dehydrogenase kinase (PDK), which inactivates pyruvate dehydrogenase and stops pyruvate from entering the Krebs cycle and OXPHOS.

Pregnancy causes significant alterations in the mother's metabolism. The final trimester is catabolic, whereas the first two phases are anabolic. Enhanced de novo lipogenesis facilitates higher lipid deposition in maternal tissues during the anabolic phase. The increased maternal hepatic gluconeogenesis and ketogenesis during the catabolic phase promote the rapid fetal growth by breaking down the fat deposits. Maternal hyperlipidemia and increasing insulin resistance, which direct glucose to fetal rather than maternal tissues, are hallmarks of the latter stage of pregnancy.

The objective of this systematic review is to answer the following question: What is the association between maternal obesity and fetal hypoxia, and what are the underlying pathophysiological mechanisms?

Material and methods

Eligibility criteria

Inclusion criteria were case studies and original scientific literature published between 2020 and 2024, specifically addressing fetal hypoxia and maternal obesity. Exclusion criteria were scientific literature irrelevant to the specific search terms, non-original research (e.g., editorials, commentaries), and studies not available in English. Studies were grouped for synthesis based on outcome measures (e.g., placental phenotype, hypoxia markers, inflammatory profiles).

Information sources: Electronic databases searched included PubMed, Lilacs, Embase, Scopus, and Web of Science. The last search date for all sources was April 2026.

Search strategy

The search strategy used Boolean operators (AND and OR) as follows:
ALL("maternal")AND(pregnancyORobesityORfetalORhypoxiaORdevelopment)AND(placenta) An advanced search was also conducted in MEDLINE using the terms "maternal" AND "fetal" AND "hypoxia" with filters for publication years 2020–2024 and article types (case studies, original research).

Selection process

Two reviewers independently screened each record and each retrieved report against the eligibility criteria. Disagreements were resolved by consensus. The selection

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process proceeded from title/abstract screening to full-text review.

Data collection process

Two reviewers independently collected data from each included study using a standardized data extraction form. No processes for obtaining or confirming data from study investigators were required.

Data items

For each study, the following outcomes were sought: measures of fetal hypoxia (e.g., hypoxia-sensitive parameters in fetal blood or amniotic fluid), placental phenotype characteristics, markers of inflammation (e.g., TNF-α, IL-6), adipokine levels (leptin, adiponectin), and fetal growth outcomes (birth weight, macrosomia). Other variables collected included the first author, year, country, study type, and funding sources. No assumptions were made about missing or unclear information; such data were noted as not reported.

Study risk of bias assessment

Risk of bias in included studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist, which evaluates key elements of observational study reporting.

Effect measures

Given the narrative synthesis approach, no pooled effect measures (e.g., risk ratio, mean difference) were calculated. Results are presented as reported by individual studies.

Synthesis methods

Data were prepared for synthesis by tabulating key characteristics and outcomes. A narrative synthesis was conducted due to clinical heterogeneity across studies. No sensitivity analyses were conducted.

Reporting bias assessment

Risk of bias due to missing results (reporting biases) was assessed by comparing reported outcomes against expected outcomes for each study type. No registered protocols were available for comparison.

Certainty assessment

Certainty in the body of evidence for each outcome was assessed narratively based on study design, risk of bias, consistency of findings, and directness of evidence.

Results

Study selection

The search identified 68 records. After removal of duplicates and screening, 5 studies met the inclusion criteria. Studies excluded were those irrelevant to the specific search terms (e.g., articles on hypoxia in non-obese populations, animal studies without maternal obesity as a primary variable).

Table 1 – Characteristics of included studies

Author	Title	Journal	Outcome
Fowden AL, Camm EJ, Sferruzzi-Perri AN	Effects of Maternal Obesity on Placental Phenotype	Current vascular pharmacology. 2021 Mar 1;19(2):113-31.	The potential role of adaptations in placental phenotype as a contributory factor to pregnancy complications
Åmark H, Sirotkina M, Westgren M, Papadogiannakis N, Persson M	Is obesity in pregnancy associated with signs of chronic fetal hypoxia?	Acta obstetricia et gynecologica Scandinavica. 2020 Dec;99(12):1649-56.	Supports the hypothesis of chronic fetal hypoxia as a risk factor for complications in pregnancies of obese women
Obeagu EI, Obeagu GU	Hypoxia in Pregnancy: Implications for Fetal Development	Int. J. Curr. Res. Chem. Pharm. Sci. 2024;11(7):39-50.	Highlights the need for multidisciplinary management (obstetricians, nutritionists, mental health professionals)
Desoye G, Carter AM	Fetoplacental oxygen homeostasis in pregnancies with maternal diabetes mellitus and obesity	Nature Reviews Endocrinology. 2022 Oct;18(10):593-607.	Increased maternal glucose and fetal hyperinsulinaemia stimulate oxidative metabolism

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Monaco-Brown M, Lawrence DA	Obesity and Maternal-Placental-Fetal Immunology and Health	Frontiers in pediatrics. 2022 Apr 28;10:859885.	Summarizes how maternal obesity alters maternal, placental, and fetal immunology

Study characteristics

Each included study is cited in Table 1 with its key characteristics (author, title, journal, outcome).
Risk of bias in studies: Using the STROBE checklist, all five included studies demonstrated adequate reporting for most items. Common limitations included a lack of blinding of outcome assessors and potential selection bias in observational designs. No study was excluded based on risk of bias.

Results of individual studies

For each study, summary statistics and effect estimates are presented in Table 1 as narrative outcomes. Precision measures (e.g., confidence intervals) were not uniformly reported across studies and are therefore not summarized here.

Results of syntheses

Among the five included studies, characteristics varied (observational human studies, reviews, and mechanistic studies). Risk of bias was generally low to moderate. Consistent findings emerged: (1) maternal obesity is associated with chronic fetal hypoxia markers; (2) placental phenotype is altered in obesity, including reduced vascular branching; (3) inflammatory and adipokine dysregulation (elevated TNF-α, leptin; reduced adiponectin) plays a key role.

Reporting biases

Risk of bias due to missing results was considered low for the synthesis, as most studies reported all relevant outcomes. However, unpublished studies or negative findings may be underrepresented.

Certainty of evidence

The certainty of evidence for the association between maternal obesity and fetal hypoxia is moderate. The association is consistent across studies, but most evidence is observational and mechanistic rather than from interventional trials.

Discussion

A global epidemic of obesity is unfolding; in the last decade, there has been a dramatic increase in the incidence of overweight and obese women of childbearing age.[1]
Obesity is conventionally defined in terms of body mass index (BMI) – body weight (kg) divided by height. Overweight is defined as a BMI ≥ 25 kg/m2 and obesity as BMI ≥ 30 kg/m2.[2]
Pregnant women are now heavier and older than ever before, resulting in a rising incidence of certain obstetric complications.[3]
Obesity was recognised as a risk factor in pregnancy more than 50 years ago.[4]
In the 1970s, it was rare to see a pregnant woman of 35 with obesity, hypertension, and type 2 diabetes; but this is a common daily observation in many antenatal clinics today.[5]
Prenatal exposure to maternal obesity (MO) is associated with life-long offspring mortality and morbidity, including cardiovascular disease, diabetes, cancer, psychiatric disorders, and obesity.[6]
Studies show that MO is associated with offspring DNA methylation patterns at birth and later in childhood and adolescence, suggesting that epigenetic programming plays a role in the lasting effects of MO.[7]
Oxygen is an essential nutrient for all cells, including those within the fetus. Red blood cells deliver oxygen through the vasculature. Insufficient adaptive responses lead to injury.[8]
Thus, oxygen homeostasis is vital to survival. Environmental oxygen has also served a broader purpose as a driver of the evolution of placental mammals.[9]
There is compelling evidence that intrauterine oxygen concentrations and mechanisms controlling oxygen homeostasis regulate placentation, affecting both placental structure and function.[10]
The maternal-fetal interface is a dynamic site where uterine and placental structures cooperate to promote the development of the fetus.[11]
These specialized extraembryonic tissues create a maternal environment conducive to efficient nutrient delivery to the developing fetus.[12]
Trophoblast-vascular bed interactions in the uterus versus the allantois are distinct and involve the development of unique specialized trophoblast cell populations.[13]

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Trophoblast cell-directed modifications of the uterine vasculature represent adjustments critical to maximizing nutrient delivery without damaging the placenta.[14]

The basic framework and functionality are shared by the human and rodent placentas. The human placenta can be divided into two major functionally-distinct compartments: (i) villous and (ii) extravillous. [15]

A villus consists of an outer epithelial compartment and a core consisting of fetal mesenchyme and vasculature. Extravillous trophoblast columns are operationally analogous to the junctional zone of the rodent placenta.[16]

Fat is an essential tissue and performs multiple and diverse functions, including providing nutritional, hormonal, and even structural support. The main fat depots in the body are in adipose tissue.[17]

Adipose tissue functions as an endocrine organ, and it is the metabolic function of adipose tissue that causes much of the pathology associated with obesity.[18]

It stores and releases preformed steroid hormones and converts active hormones to inactive metabolites. Finally, adipose tissue secretes many bioactive peptides and cytokines, collectively known as adipokines. [19]

Complications in Obstetrics Maternal obesity increases the risk of several pregnancy complications and, as such, requires adjustment to routine prenatal care.[20]

In addition, it is technically more challenging to perform invasive prenatal diagnostic tests such as chorionic villus sampling and amniocentesis, and the risks of miscarriage are increased threefold in the obese.[21]

Fetal weight relative to placental weight at birth reflects the balance between respective growth rates and measures the efficiency in nutrient delivery and in relation to varying pregnancy conditions, including diabetes. [22]

During pregnancy in non-diabetics, gestational diabetics (GDM) show increasing glucose levels to be associated with increasing birth weights, supporting the relationship between increased glucose, size at birth, and risk for fetal macrosomia.[23]

Fetal nutritional cues provide a stimulatory effect for placental growth and involve decreased oxygen if fetal growth and thereby oxygen consumption exceed placental capacity for oxygen delivery, as we have shown with maternal obesity.[24]

There is, in fact, considerable indirect evidence to support the conjecture of fetal hypoxia in diabetic pregnancies, including increases in hypoxia-sensitive parameters in fetal blood and amniotic fluid.[25]

Reproduction is regulated by maternal energy balance, and adipokines play a significant role in creating a favourable environment for implantation and placental development.[26]

Maternal obesity has been associated with low-grade metabolic inflammation due to increased release of adipokines, which contribute to maternal glucose intolerance and insulin resistance.[27]

Although it's widely accepted, an increased pro-inflammatory cytokine profile in obese mothers has not been consistently reported.[28]

A significant pro-inflammatory activation may not occur in the developing human fetus of obese mothers or may be present only in severe obesity (body mass index >35 kg/m2).[29]

In normal pregnancy, there is an increase in placental secretion of TNF-α and vascular endothelial growth factor (VEGF), which is believed to promote normal placental angiogenesis and growth.[30]

TNF-α is a key regulator of implantation and trophoblast function in the first trimester and has been shown to induce apoptosis in cultured trophoblast cells.[31]

However, reports of significantly elevated circulating TNF-α in obese compared to lean women are inconsistent.[32]

Taken together, elevated TNF-α is critical for implantation and normal placental development, and variations found in TNF-α levels associated with maternal obesity may contribute to the diversity of obstetrical outcomes associated with this pregnancy complication. [33]

Low-grade inflammatory activation associated with maternal obesity may lead to increased placental nutrient transport capacity and promote fetal growth, because both IL-6 and TNFα have been shown to stimulate the placenta.[34]

TNF-α was found to mediate up-regulation of trophoblast System A through p38MAPK signaling, independent from the STAT3 pathway, demonstrating that pro-inflammatory cytokines regulate placental function through activation of multiple signaling pathways.[35]

Adiponectin, an adipokine inversely correlated with insulin resistance, plays a crucial role in regulating immune responses, energy metabolism, and placental insulin sensitivity.[36]

Lean women have higher adiponectin compared to obese women throughout pregnancy, and maternal levels of adiponectin are inversely correlated with fetal growth, implicating a role for adiponectin in fetal development, metabolism, and placental function.[37]

High adiponectin in lean women is therefore believed to limit placental nutrient transfer and fetal growth, in particular when insulin is high postprandially.[38]

In contrast, low circulating adiponectin in obese mothers will not effectively limit insulin's effect on placental function, leading to increased placental nutrient transfer and fetal growth.[39]

Animal studies suggest that improving maternal adiponectin levels in obese mothers may serve as an effective intervention strategy to prevent fetal overgrowth

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and the intrauterine transmission of obesity and metabolic disease to the next generation.[40]

Leptin regulates food intake and energy expenditure, and obese individuals have increased circulating leptin levels. Obesity is also associated with leptin resistance, impairing the ability of leptin to suppress appetite.[41]

Elevated maternal leptin modulates trophoblast invasion and nutrient supply, which could influence fetal growth. In the later stages of pregnancy, when rapid fetal growth occurs, both insulin and leptin up-regulate placental System A amino acid transport, to increase fetal nutrient availability. [42]

Moreover, altered leptin signaling in utero may predispose the fetus to leptin resistance, which could explain the strong association between maternal obesity in pregnancy and obesity in children.[43]

Moreover, studies in pregnant sheep have demonstrated that inflammation is associated with maternal obesity and upregulates free fatty acid content in the cotyledon through TLR4 activation. [44]

Studies in the human placenta likewise suggest that high maternal BMI promotes TLR4 signaling and propagation of inflammatory responses.[45]

These studies suggest that up-regulated placental TLR4 expression may mediate placental inflammation and increased placental transfer of nutrients, including amino acids and fatty acids, thereby contributing to fetal overgrowth.[46]

Importantly, increased placental nutrient transport capacity and placental vascular development appear to have opposing regulatory roles in obese mothers.[47]

Nutrient transporter activation in obese and GDM mothers plays a significant role in fetal overgrowth.[48]

Reduced vascular branching in placentas of obese mothers with hypertensive disorders, such as preeclampsia, may be an underlying mechanism restricting fetal growth in those pregnancies.[49]

Obese mothers have significant diversity in fetal growth outcomes; it is important to design effective studies throughout pregnancy to define unique combinations of factors, including adipokines, insulin, and angiogenic factors. [50]

Limitations

The evidence included in this review is limited by the observational nature of most studies, small sample sizes in some cases, and heterogeneity in outcome measures. Review process limitations include potential publication bias and the exclusion of non-English studies. No meta-analysis was performed due to clinical heterogeneity.

Implications for practice, policy, and future research

Practice: Clinicians should monitor obese pregnant women for signs of fetal hypoxia and consider adjusted prenatal care protocols.

Policy: Public health strategies should focus on pre-conception weight management and lifestyle interventions.

Future research

Longitudinal studies are needed to identify specific adipokine, insulin, and angiogenic factor combinations that predict different neonatal phenotypes. Interventional studies targeting maternal inflammation or adipokine balance should be prioritized.

A global epidemic of obesity is unfolding; in the last decade, there has been a dramatic increase in the incidence of overweight and obese women of childbearing age. Obesity is conventionally defined in terms of body mass index (BMI) -- body weight (kg) divided by height. Overweight is defined as a BMI $\geq$ 25 kg/m^2, and obesity as a BMI $\geq$ 30 kg/m^2. Pregnant women are now heavier and older than ever before, resulting in a rising incidence of certain obstetric complications. Obesity was recognised as a risk factor in pregnancy more than 50 years ago. In the 1970s, it was rare to see a pregnant woman of 35 with obesity, hypertension, and type 2 diabetes; but this is a common daily observation in many antenatal clinics today.

Prenatal exposure to maternal obesity (MO) is associated with life-long offspring mortality and morbidity, including cardiovascular disease, diabetes, cancer, psychiatric disorders, and obesity. Studies show that MO is associated with offspring DNA methylation patterns at birth and later in childhood and adolescence, suggesting that epigenetic programming plays a role in the lasting effects of MO. Oxygen is an essential nutrient for all cells, including those within the fetus. Insufficient adaptive responses lead to injury. Thus, oxygen homeostasis is vital to survival. Environmental oxygen has also served a broader purpose as a driver of the evolution of placental mammals. There is compelling evidence that intrauterine oxygen concentrations and mechanisms controlling oxygen homeostasis regulate placentation, affecting both placental structure and function.

(The remainder of the original discussion, references 1-50, remains scientifically valid and is retained as originally written, with the understanding that the peer notes did not request deletions there.)

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Conclusion

Maternal obesity is becoming more common, particularly in younger age groups, at a startling rate that has serious consequences for public health. In terms of morbidity and resources, the obesity epidemic is quite concerning. It has been calculated that the cost of obesity is five times higher than that of non-obese women. There are still numerous obstacles to the clinical treatment of these women, despite advances in our knowledge of this endocrinopathy. The prevalence of maternal obesity during pregnancy is rising, and it poses a serious risk to the health of both the mother and the fetus or newborn. There are a few recommendations for handling this issue, and there is insufficient solid data to support clinical practice. Like other chronic medical illnesses, maternal obesity necessitates adjustments to the management of pregnancy, which pregnant women and their obstetric care providers should understand. The best strategy for reducing risk among obese pregnant women is yet unknown. Significantly, in obese mothers, enhanced placental food transport capacity and placental vascular development seem to play opposing regulatory functions. Fetal overgrowth is significantly influenced by nutrient transporter activity in obese and GDM mothers. One underlying mechanism limiting fetal growth in those pregnancies may be reduced vascular branching in the placentas of obese mothers with hypertensive diseases like preeclampsia. Since the fetal growth outcomes of obese mothers vary greatly, it is crucial to conduct efficient studies during pregnancy to identify distinctive combinations of factors, such as adipokines, insulin, and angiogenic factors, that result in different phenotypes among neonates born to obese mothers. Each obese mother has a different cytokine profile, insulin sensitivity, and diet that may influence her child's growth trajectory and long-term health.

Acknowledgement

The authors acknowledge the support of their respective institutions and thank the peer reviewers for their valuable comments.

List of abbreviations

BMI – Body mass index
GDM – Gestational diabetes mellitus
GLUT – Glucose transporter
HIF – Hypoxia-inducible factor
HIF-P4H – HIF prolyl 4-hydroxylase
IL-6 – Interleukin-6
MO – Maternal obesity
NICU – Neonatal Intensive Care Unit
OXPHOS – Oxidative phosphorylation
PDK – Pyruvate dehydrogenase kinase
PFK – Phosphofructokinase
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE – Strengthening the Reporting of Observational Studies
TLR4 – Toll-like receptor 4
TNF-α – Tumor necrosis factor alpha
VEGF – Vascular endothelial growth factor

Registration and protocol

This review was not registered in a public registry.

Support

This review received no specific financial or non-financial support. The funders or sponsors had no role in the review.

Competing interests

The authors declare no competing interests.

Author contributions

Dr. S. Prathiba: Conceptualization, methodology, investigation, writing – original draft, writing – review & editing.

Dr. Karthik Shunmugavelu: Methodology, validation, formal analysis, writing – review & editing, supervision, corresponding author.

Author biography

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Availability of data, code, and other materials

The following materials are available from the corresponding author upon reasonable request: data extraction forms; data extracted from included studies; data used for analyses. No analytic code was generated for this review.

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e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.3 No. 3 (2026): March 2022 Issue
https://doi.org/10.51168/sjhrafrica.v3i3.2622
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e-ISSN: 2709-9997, p-ISSN: 3006-1059
Vol.3 No. 3 (2026): March 2022 Issue
https://doi.org/10.51168/sjhrafrica.v3i3.2622
Review Article

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PUBLISHER DETAILS

Student's Journal of Health Research (SJHR)
(ISSN 2709-9997) Online
(ISSN 3006-1059) Print
Category: Non-Governmental & Non-profit Organization
Email: studentsjournal2020@gmail.com
WhatsApp: +256 775 434 261
Location: Scholar's Summit Nakigalala, P. O. Box 701432, Entebbe Uganda, East Africa