Research Article

Visceral Fat As The Main Obesity Index That Determines The Occurrence of Adipose Tissue Insulin Resistance

Liong Boy Kurniawan[1*], Lita Paramitha Apriani[2], Nursin Abdul Kadir[1], Nurahmi Nurahmi[1], Muhammad Iqbal Basri[3], Aminuddin Aminuddin[4]

[1]*Clinical Pathology Department, Medical Faculty, Hasanuddin University, Makassar, Indonesia*
[2]*Residency Program in Clinical Pathology, Medical Faculty, Hasanuddin University, Makassar, Indonesia*
[3]*Anatomy Department, Medical Faculty, Hasanuddin University, Makassar, Indonesia*
[4]*Nutrition Department, Medical Faculty, Hasanuddin University, Makassar, Indonesia*

Article Info

[*]***Corresponding Author:***
Liong Boy Kurniawan MD, Ph.D
Medical Faculty, Hasanuddin University,
Perintis Kemerdekaan Road, Makassar,
South Sulawesi, Indonesia,
https://orcid.org/0000-0002-2633-0441
E-mail: liongboykurniawan@yahoo.com

Keywords
Visceral Fat, Obesity Index, Adipo-IR

Abstract

Background: Insulin resistance may occur in various organs, including adipose tissue, which causes increased lipolysis and blood free fatty acids (FFA). Insulin resistance in adipose tissue is commonly assessed using the Adipose Tissue Insulin Resistance (Adipo-IR) index, calculated using fasting insulin and FFA levels. This study aimed to evaluate which obesity index has the best predictive value to determine Adipo-IR.

Methods: This cross-sectional study is conducted on 80 non-diabetic adult subjects. Measurements and assessments of the relationship between obesity indices and Adipo-IR values were performed.

Results: Waist circumference ($r = 0.275$, $p = 0.013$), BMI ($r = 0.318$, $p = 0.004$), visceral fat ($r = 0.334$, $p = 0.002$), and body fat percentage ($r = 0.246$, $p = 0.028$) were all significantly correlated with Adipo-IR. The area under the curve (AUC) showed that visceral fat had the most significant predictive value of insulin resistance in adipose tissue compared to BMI, waist circumference, and body fat (AUC = 0.690 vs 0.663 vs 0.620 vs 0.570). Subjects with visceral fat values in the fourth quartile had a 6-fold risk of experiencing insulin resistance in adipose tissue compared to subjects in quartile 1 (OR = 6, $p = 0.014$, 95% CI 1.324-27.191).

Conclusions: The Adipo-IR index increases with the value of the obesity index. Visceral fat has the highest predictive value in determining the occurrence of adipose tissue insulin resistance.

Introduction

Insulin resistance is marked by a decreased response of different tissues sensitive to insulin activity, resulting in increased insulin production to compensate for the reduced effectiveness of insulin action [1]. Insulin works by increasing the glucose entry from the blood into peripheral tissues (liver, muscle, adipose tissue) and inhibiting the process of gluconeogenesis in the liver [2]. Increased adipose tissue lipolysis due to insulin resistance results in a rise in the generation of free fatty acids (FFA), which are subsequently released into the bloodstream [1,2].

The prevalence of obesity, a worldwide issue, is rising annually. The hallmark of obesity is the increased buildup of fat in the body, which can be caused by either hyperplasia or hypertrophy of adipocyte cells [3]. White adipose tissue is a fat tissue mainly found in visceral and subcutaneous tissues, is endocrine active, and has an essential role in insulin resistance development [4]. In obesity, increased formation of FFA and dietary fat trigger lipotoxicity, which can cause worsening insulin resistance, mainly in the skeletal muscle and liver [3-5]. Adipose tissue produces a variety of adipocyte-related cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, which can also reduce insulin sensitivity and induce lipolysis [6].

There is a relationship between various obesity indices, both traditional waist circumference (WC), body mass index (BMI), and non-traditional ones such as visceral fat (VF) and body fat percentage (BF), with the presence of insulin resistance, especially in the liver and muscle [7-9]. The adipose tissue insulin resistance (Adipo-IR) index measures adipose tissue insulin resistance, calculated by multiplying fasting insulin by FFA levels. [10]. This study intends to establish which obesity indicator has the most predictive value to detect adipose tissue insulin resistance and to investigate the association between multiple obesity indices, particularly WC, BMI, VF, and BF, with the Adipo-IR index.

Methods

Study Population

This was cross-sectional study was conducted on 80 non-diabetic adult subjects who voluntarily participated by agreeing to the informed consent. Sampling and laboratory examinations were performed at Hasanuddin University Hospital from August to September 2024. The study population was clinical clerkship students, medical faculty residents, and students of the Hasanuddin University Biomedical Sciences master's program who were willing to participate. Adult participants who were at least eighteen years old met the inclusion criteria. Subjects with fasting blood glucose levels (FBG) ≥126 mg/dL and or oral glucose tolerance test (OGTT) ≥200 mg/dL, having a history of diabetes mellitus (DM), taking lipid-lowering drugs, and experiencing inflammation or infection, were excluded. This study received an ethical approval recommendation from the Hasanuddin University Research Ethics Committee with No: 649/UN4.6.4.5.31/PP36/2024.

Obesity Index Measurement and Laboratory Procedure

Obesity indices measured include WC, BMI, VF, and BF. After measuring height and body weight (BW), BMI was calculated using the formula BMI = BW/Height^2. The measurement of waist circumference was taken halfway between the lower border of the 12th rib and the iliac crest. BF and VF measurements were performed using the bioelectrical impedance analysis (BIA) method. BW (coefficient variation (CV) = 0.09%), BF (CV = 1.04%), and VF (CV = 0%) measurements were performed using the Tanita BC-541 (Japan) device. The study subjects were fasted for 8-10 hours at night, and then blood samples were taken at 8 am the next day, followed by an OGTT test. FBG and OGTT examinations were carried out, according to standard protocols. A 5cc fasting blood sample was taken, then the serum was separated. Glucose examination was carried out immediately after sampling, and then the remaining fasting serum sample was stored in aliquot form at -20 °C for further examination of insulin and FFA. Glucose examination was performed using the enzymatic-colorimetry method using the Abx Pentra 400 (Horiba, United States), while insulin was examined using the electrochemiluminescence immunoassay (ECLIA) method with the Cobas e411 (Roche, Germany). Using a kit from MyBioSource (United States), the enzyme-linked immunosorbent assay (ELISA) method was used to measure the serum FFA levels. The formula = (FBG (mg/dL) x Insulin (mIU/L)/405) was used to measure the homeostatic model assessment of insulin resistance index (HOMA-IR). FFA (mmol/L) x Insulin (mIU/L) was the formula used to calculate the Adipo-IR index. Adipo-IR values ≥75th percentile are used to establish the occurrence of adipose tissue insulin resistance. Subjects with Adipo-IR values below the 75th percentile were classified as not experiencing insulin resistance in adipose tissue. The 75th percentile value of Adipo-IR in this study was 5.84.

Statistical Analysis

The numerical data normality was evaluated by the Kolmogorov-Smirnov test. The variables of age, WC, and BF were normally distributed, while other parameters, including systolic, diastolic blood pressure, FBG, insulin, FFA, HOMA-IR, Adipo-IR index, VF, and BMI, were not normally distributed. The Spearman Correlation test was used to assess the association between the Adipo-IR index and the other parameters. Analysis with the receiver operating characteristic (ROC) curve was conducted to analyze the role of various obesity indices as adipose tissue insulin resistance predictors, followed by an assessment of the area under the curve (AUC) and determination of the best cut-off value (which had the highest combination of sensitivity and specificity) in predicting insulin resistance in adipose tissue. The Odds ratio (OR) value of the increasing risk of insulin resistance in adipose tissue along, with increasing quartiles of VF values, was performed with the Fisher-Exact or Chi-Square test.

Results

A total of 80 volunteers, consisting of 38 (47.5%) men and 42 (52.5%) women, were willing to join the research. The research subjects' basic characteristics are shown in Table 1. The average age of the research subjects was 31.69±4.09 years, ranging between 21 to 40 years.

Table 1: Basic Characteristics of Study Subjects.

Variables	Mean±SD	Median (Min-Max)
Age (years)	31.69±4.09	31 (21-40)
Systole (mmHg)	116.20±8.52	120 (90-130)
Diastole (mmHg)	76.11±7.48	80 (60-100)
FBG (mg/dL)	97.23±10.83	95.50 (69-123)
Insulin (mIU/L)	15.41±14.08	11.52 (4.31-70.64)
FFA (mmol/L)	0.28±0.36	0.15 (0.01-2.15)
HOMA-IR (unit)	3.82±3.97	2.59 (0.98-25.47)
Adipo-IR (unit)	4.13±5.63	1.99 (0.05-24.34)
BMI (kg/m2)	25.62±4.79	25.05 (15.30-45)
WC (cm)	89.52±11.01	90 (61-133)
BF (%)	29.25±6.50	29.05 (12-43.80)

The correlation between the Adipo-IR index and other parameters is shown in Table 2. From weakest to strongest, the Adipo-IR index correlates with BF (r = 0.246), WC (r = 0.275), BMI (r = 0.318), and VF (r = 0.334). It also exhibits a substantial association with HOMA-IR (r = 0.522).

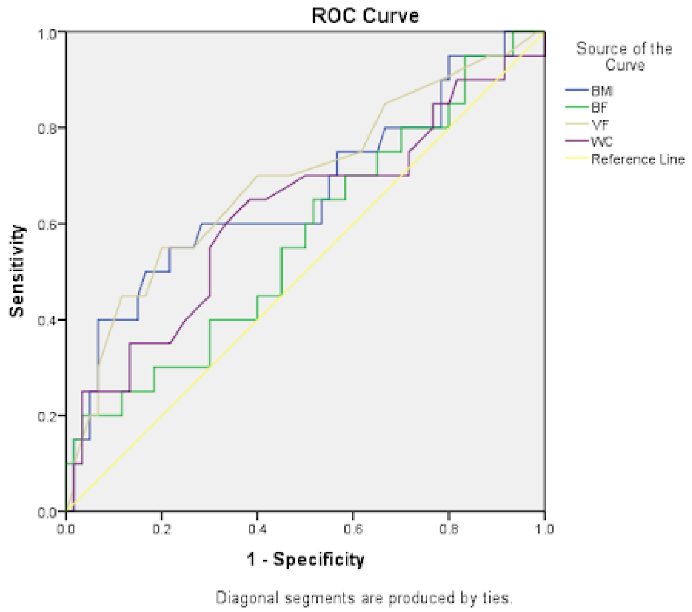
Table 2: Correlation Between Various Variables with Adipo-IR Index.

Variables	Adipo-IR Index	
	r	p*
Age	0.206	0.067
Systole	0.154	0.171
Diastole	0.013	0.911
FBG	0.13	0.251
Insulin	0.521	<0.001
FFA	0.904	<0.001
HOMA-IR	0.522	<0.001
BMI	0.318	0.004
WC	0.275	0.013
BF	0.246	0.028

*Spearman Correlation Test

The ROC curve below displays the ability of various obesity parameters to determine the occurrence of insulin resistance in adipose tissue (Figure 1).

Figure 1: ROC Curve of Obesity Indices as Adipose Tissue Insulin Resistance Predictors.



The AUC value shows that VF (AUC = 0.690, cut off = 8.5) and BMI (AUC = 0.663, cut off = 26.95 cm) have the strongest predictive ability in determining the occurrence of insulin resistance in adipose tissue (Table 3).

Table 3: AUC Values and Best Cut-off Values of Obesity Indices in Determining the Occurrence of Insulin Resistance in Adipose Tissue.

Variables	AUC	p	95% CI	Cut-off	Sensitivity	Specificity
BMI	0.663	0.03	0.513-0.813	26.95	0.55	0.783
WC	0.62	0.108	0.467-0.774	91.5	0.65	0.617
BF	0.57	0.351	0.422-0.718	28.3	0.65	0.483
VF	0.69	0.011	0.547-0.833	8.5	0.7	0.6

VF, the obesity index, which has the best predictor value for assessing adipose tissue insulin resistance, will then be divided into 4 quartiles. The risk (OR) of adipose tissue insulin resistance in each quartile is assessed by comparing it with the risk in quartile 1. Those in the highest quartile had 6 times higher risk to having adipose tissue insulin resistance compared to the in the lowest quartile (Table 4).

Table 3: AUC Values and Best Cut-off Values of Obesity Indices in Determining the Occurrence of Insulin Resistance in Adipose Tissue.

"VF Quartiles"	Adipo IR State	Non_Adipo IR State	p OR (CI 95%)	
	n (%)	n (%)		
4 (>11)	9 (47)	10 (52.6)	0.014[1]	6.00 (1.324-27.191)
3 (8.1-11)	5 (26.3)	14 (73.7)	0.433[2]	2.38 (0.488-11.628)
2 (5.1-8)	3 (15.8)	16 (84.2)	0.570[2]	1.25 (0.222-7.051)
1 (<5)	3 (13)	20 (87)		Baseline
Total	20 (25)	60 (75)		

[1] Chi-Square Test

[2] Fisher-Exact Test

Discussion

In this investigation, a significant association was found between the Adipo-IR index and the obesity index, with the strongest correlation found in VF (r = 0.334) followed by BMI (r = 0.318), WC (r = 0.275), then BF (r = 0.246). Kim et al performed research on 205 adolescents and young adults (normoglycemia, pre-diabetes, and diabetes subjects) in the United States and described similar results with the findings that the Adipo-IR index correlated with visceral adipose tissue (r = 0.557) as measured by computed tomography (CT), BMI (r = 0.559) and BF (r = 0.529) [11]. Semnani-Azad et al performed a study on 468 non-diabetic adult subjects with a mean age of 50 years and revealed that the Adipo-IR index had correlation with WC (r = 0.520) and BMI (r = 0.560) [12]. Zhang et al in Beijing, China, conducted a study on 312 people with and without metabolic syndrome and found the Adipo-IR index associated with WC (r = 0.480) and BMI (r = 0.430) [13]. Several studies mentioned above showed similar results to the report of this study, although there are variations in the order of obesity indices and the strength of their correlations that can be caused by differences in race, average age, and clinical conditions of the subjects when compared to this study. In contrast, Kitaoka et al in Japan reported no correlation between the Adipo-IR index and BMI (r = -0.007, p>0.05) and WC (r = -0.062, p>0.05) in young female subjects (average age 20.7 years) [14]. This may be because the study population was women with an average BMI (20.3 kg/m2) and WC (71.2 cm) within the normal range.

In this study, it was found that compared to other obesity indices, VF had the strongest correlation with the Adipo-IR index. There are several things that can explain this. VF is ectopic fat classified as white adipose tissue, composed of larger adipocytes with fewer mitochondria than brown adipose tissue. VF is spread in the mesentery, omentum, and retroperitoneal space and is active both as an endocrine and metabolic organ that has a significant role in the occurrence of insulin resistance. Adipose tissue insulin resistance, especially in VF, causes suppression of insulin's ability to prevent lipolysis, contributing to the increased release of FFA into the blood [15-20]. In this study, it was found that VF had a stronger association with Adipo-IR than WC. This may be because WC measurements not only assess VF but also subcutaneous fat (SF). SF is reported to have a role quite different from VF, having protective properties against insulin resistance. Subjects with a low VF/SF ratio have better insulin sensitivity than subjects with a high VF/SF ratio [21]. WC measurements not only measure VF, which is associated with the insulin resistance state but also measure SF, which is protective against the occurrence of insulin resistance so that cumulatively, the correlation of WC (accumulation of VF and SF) with Adipo-IR is lower than the correlation of Adipo-IR with VF alone.

In this study, it was found that VF had the best predictive ability in assessing the occurrence of insulin resistance in adipose tissue (AUC = 0.690, cut off = 8.5) followed by BMI (AUC = 0.663, cut off = 26.95 kg/m2). Jiang et al, in Zhejiang, China, conducted a study on 499 subjects aged over 50 years and found that BMI (AUC = 0.770, cut off = 22.04 kg/m2 in men; AUC = 0.780, cut off = 21.77 kg/m2 in women) and WC (AUC = 0.790, cut off = 83.5 cm in men; AUC = 0.770, cut off = 84.75 cm in women) can be used as predictors of insulin resistance in peripheral tissue (Adipo-IR values above the 66.7th percentile are used to define insulin resistance in adipose tissue; cut off values 1.87 in men and 3.87 in women) [22]. The difference in AUC and cut-off values reported by Jiang et al with our study is due to differences in population characteristics and the Adipo-IR index percentile (cut-off) values in defining adipose tissue insulin resistance. However, the BMI cut-off value reported by this study (26.95 kg/m2) in predicting insulin resistance in adipose tissue is closer to the cut-off value used to define obesity in Southeast Asian countries, including Indonesia (range 25-30 kg/m2) [23]. This study also found that subjects with VF values in quartile 4 (>11) had a 6-fold increased risk of suffering from insulin resistance in adipose tissue compared to subjects with VF values in quartile 1 (<5). Increased VF mass can trigger the release of various pro-inflammatory adipokines, including leptin, IL-6, and TNF-α, that can trigger systemic insulin resistance in adipose tissue [24]. Increased lipid accumulation, especially in visceral tissue, will trigger lipotoxicity, metabolic disorders, and resistance in adipose tissue, thus triggering lipolysis, characterized by increased FFA release in the blood [25].

The cross-sectional study design of this research is one of its limitations, as it is unable to elucidate the causal relationship between the variables under investigation: therefore, future longitudinal studies are needed to establish the causality. The research subjects came from a single population, so further research is needed to involve multicenter studies with different age groups and ethnicities to generalize the findings of this study. To validate the findings of this study, more research may be done utilizing the gold standard technique for evaluating VF and BF, which is magnetic resonance imaging (MRI) or CT, since the VF measurement agreement between BIA and CT methods is moderate (r = 0.387 to 0.626) [26].

Conclusion

The Adipo-IR index increases with the value of the obesity index. Visceral fat has the highest predictive value in determining adipose tissue insulin resistance; therefore, it can be used as a routine screening protocol for assessing insulin resistance.

Author Contributions

LBK, NAK, NN, MIB, and AA conceived the study. LBK and LPA collected samples and prepared the initial draft of this manuscript. LBK, NAK, NN, MIB, and AA conducted further reviews and provided scientific input on this manuscript.

Funding

This research received funding from the Faculty of Medicine, Hasanuddin University (No: 4669/UN4.6/PT.01.05/2024).

Conflict Of Interest

None.

References

1. Lee SH, Park SY, Choi CS. Insulin resistance: from mechanisms to therapeutic strategies. Diabetes Metab J. 2022;46(1):15-37. doi:10.4093/dmj.2021.0280.
2. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther. 2022;7(1):216. doi:10.1038/s41392-022-01073-0.
3. Tong Y, Xu S, Huang L, Chen C. Obesity, and insulin resistance: pathophysiology and treatment. Drug Discov Today. 2022;27(3):822-830. doi:10.1016/j.drudis.2021.11.001.
4. An SM, Cho SH, Yoon JC. Adipose tissue and metabolic health. Diabetes Metab J. 2023;47(5):595-611.
5. Kojta I, Chacińska M, Błachnio-Zabielska A. Obesity, bioactive lipids, and adipose tissue inflammation in insulin resistance. Nutrients. 2020;12(5):1305. doi:10.3390/nu12051305.
6. Martins LM, Oliveira ARS, Cruz KJC, Torres-Leal FL, Marreiro DDN. Obesity, inflammation, and insulin resistance. Brazilian Journal of Pharmaceutical Sciences. 2014;50(4):677–692.
7. Lim SM, Choi DP, Rhee Y, Kim HC. Association between obesity indices and insulin resistance among healthy korean adolescents: the js high school study. PLoS One. 2015;10(5):e0125238. doi:10.1371/journal.pone.0125238.
8. Kurniawan LB, Bahrun U, Hatta M, Arif M. Body mass, total body fat percentage, and visceral fat level predict insulin resistance better than waist circumference and body mass index in healthy young male adults in indonesia. J Clin Med. 2018;7(5):96. doi:10.3390/jcm7050096.
9. Kurniawan LB, Syamsir B, Rahman IA, Adnan E, Esa T, Widaningsih Y, et al. Anthropometric features in predicting insulin resistance among non-menopausal indonesian adult females. Rom J Intern Med. 2020;58(3):168-172. doi:10.2478/rjim-2020-0015.
10. Gastaldelli A. Measuring and estimating insulin resistance in clinical and research settings. Obesity (Silver Spring). 2022;30(8):1549-1563. doi:10.1002/oby.23503.
11. Kim JY, Bacha F, Tfayli H, Michaliszyn SF, Yousuf S, Arslanian S. Adipose tissue insulin resistance in youth on the spectrum from normal weight to obese and from normal glucose tolerance to impaired glucose tolerance to type 2 diabetes. Diabetes Care. 2019;42(2):265-272. doi:10.2337/dc18-1178.
12. Semnani-Azad Z, Connelly PW, Bazinet RP, Retnakaran R, Jenkins DJA, Harris SB, et al. Adipose tissue insulin resistance is longitudinally associated with adipose tissue dysfunction, circulating lipids, and dysglycemia: the promise cohort. Diabetes Care. 2021;44(7):1682-1691. doi:10.2337/dc20-1918.
13. Zhang K, Pan H, Wang L, Yang H, Zhu H, Gong F. Adipose tissue insulin resistance is closely Associated with Metabolic Syndrome in Northern Chinese Populations. Diabetes Metab Syndr Obes. 2021;14:1117-1128. doi:10.2147/DMSO.S291350.
14. Kitaoka K, Tsuboi A, Minato-Inokawa S, Honda M, Takeuchi M, Yano M, et al. Determinants and correlates of adipose tissue insulin resistance index in japanese women without diabetes and obesity. BMJ Open Diabetes Research and Care. 2020;8:e001686. doi: 10.1136/bmjdrc-2020-001686.
15. Reyes-Farias M, Fos-Domenech J, Serra D, Herrero L, Sánchez-Infantes D. White adipose tissue dysfunction in obesity and aging. Biochem Pharmacol. 2021;192:114723. doi:10.1016/j.bcp.2021.114723.
16. Ahmed B, Sultana R, Greene MW. Adipose tissue and insulin resistance in obese. Biomed Pharmacother. 2021;137:111315. doi:10.1016/j.biopha.2021.111315.
17. Janochova K, Haluzik M, Buzga M. Visceral fat and insulin resistance - what we know?. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2019;163(1):19-27. doi:10.5507/bp.2018.062.
18. Smith U, Kahn BB. Adipose tissue regulates insulin sensitivity: role of adipogenesis, de novo lipogenesis and novel lipids. J Intern Med. 2016;280(5):465-475. doi:10.1111/joim.12540.
19. Zhang M, Hu T, Zhang S, Zhou L. Associations of different adipose tissue depots with insulin resistance: a systematic

review and meta-analysis of observational studies. Sci Rep. 2015;5:18495. doi:10.1038/srep18495.
20. Chait A, Den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Front Cardiovasc Med. 2020;7:22. doi:10.3389/fcvm.2020.00022.
21. Caprio S, Perry R, Kursawe R. Adolescent obesity and insulin resistance: roles of ectopic fat accumulation and adipose inflammation. Gastroenterology. 2017;152(7):1638-1646. doi:10.1053/j.gastro.2016.12.051.
22. Jiang J, Cai X, Pan Y, Du X, Zhu H, Yang X, et al. Relationship of obesity to adipose tissue insulin resistance. BMJ Open Diabetes Res Care. 2020;8(1):e000741. doi:10.1136/bmjdrc-2019-000741.
23. Tham KW, Abdul Ghani R, Cua SC, Deerochanawong C, Fojas M, Hocking S, et al. Obesity in south and southeast asia-a new consensus on care and management. Obes Rev. 2023;24(2):e13520. doi:10.1111/obr.13520.
24. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity?. Curr Opin Endocrinol Diabetes Obes. 2012;19(2):81-87. doi:10.1097/MED.0b013e3283514e13.
25. Nakamura M. Lipotoxicity as a therapeutic target in obesity and diabetic cardiomyopathy. J Pharm Pharm Sci. 2024;27:12568. doi:10.3389/jpps.2024.12568.
26. Xu Z, Liu Y, Yan C, Yang R, Xu L, Guo Z, et al. Measurement of visceral fat and abdominal obesity by single-frequency bioelectrical impedance and ct: a cross-sectional study. BMJ Open. 2021;11(10):e048221. Doi:10.1136/bmjopen-2020-048221.