



## Editorial

- **Nutritional care is a human right: incorporating principles into clinical practice**

## Clinical Nutrition : Nutrition & Metabolism

- **Effect of oral vitamin E supplementation on lipid profile in diabetes mellitus: evidence based case report**
  - **Effect of omega-3 supplementation on osteoarthritis: An evidence-based case report**
  - **The correlation of folic acid and homocysteine serum with vascular density and retinal non-perfusion area in diabetic retinopathy**
- **Enteral nutrition with medium-chain triglyceride compared to total parenteral nutrition in patient with chylothorax: an evidence based case report**
- **The impact of omega-3 on recurrent seizures in epileptic patients: A case study with evidence-based approaches**

## Community Nutrition: Nutrition Through Life Cycle

- **Effect of smartphone application with reminder on total fluid intake adequacy and hydration status among adults in Bontang, East Kalimantan**
- **The association between knowledge and attitude towards nutrition fact panels (NFP) with sugar intake of the Indonesian adolescents**
  - **Nutrient-rich food index 9.3 score and food choice values among female online food delivery users during COVID-19 pandemic**
- **Analysis of macronutrient and micronutrient intake with the incidence of stunting and wasting in toddlers 0-59 months of age at public health center in Bojong, Bogor regency, Indonesia**
- **Association between consumption of ultra-processed foods and beverages with nutritional status of private senior high school students in Pontianak, West Kalimantan, Indonesia**
- **Overview of fluid and macronutrient intake, knowledge and attitudes and eating behavior among private university medical students in Jakarta**

## Food & Nutrition : Functional Food

- **The role of polyphenols in atopic dermatitis: A literature review**

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# Table of Content

# Page

Volume 07, Issue 02, February 2024 | page 1 – 117, | eISSN: 2580-7013

## Editorial

Pansawira. P	<b>Nutritional care is a human right: incorporating principles into clinical practice</b>	<b>i</b>
--------------	---	----------

## *Clinical Nutrition : Nutrition & Metabolism*

Wulandari. I. S Sutanto. K	<b>Effect of oral vitamin E supplementation on lipid profile in diabetes mellitus: evidence based case report</b>	<b>1</b>
-------------------------------	---	----------

Ferdi. J Sunardi. D	<b>Effect of omega-3 supplementation on osteoarthritis: An evidence-based case report</b>	<b>9</b>
------------------------	---	----------

Dharma. A. G Wildan. A Prihatningtias. R Rahmi F. L Nugroho. T Saubig. A. N Rikiandraswida. Z	<b>The correlation of folic acid and homocysteine serum with vascular density and retinal non- perfusion area in diabetic retinopathy</b>	<b>18</b>
---	---	-----------

Tedjaatmadja. C Wulandari. Y	<b>Enteral nutrition with medium-chain triglyceride compared to total parenteral nutrition in patient with chylothorax: an evidence based case report</b>	<b>26</b>
---------------------------------	---	-----------

Wijayanthie. N Lestari. W	<b>The impact of omega-3 on recurrent seizures in epileptic patients: A case study with evidence- based approaches</b>	<b>35</b>
------------------------------	--	-----------

## *Clinical Nutrition : Nutrition Through Life Cycle*

Sari. H. E. P Sunardi. D Sutanto. K Chandra. D. N Friska. D Insani. P. E. C	<b>Effect of smartphone application with reminder on total fluid intake adequacy and hydration status among adults in Bontang, East Kalimantan</b>	<b>46</b>
--	--	-----------

Wulandari. C Sumardiyono Febrinasari. R. P	<b>The association between knowledge and attitude towards nutrition fact panels (NFP) with sugar intake of the Indonesian adolescents</b>	<b>54</b>
Palupi. N. S Chandra. D. N Februhartanty . J Khusun. H Hanisa. N Dewi. D. K	<b>Nutrient-rich food index 9.3 score and food choice values among female online food delivery users during COVID-19 pandemic</b>	<b>65</b>
Widyawardani. N Bustamam. N Aprilia C. A Hardini. N Prasetio P. O Yusuf K. N Harahap. M. F. R Raihan R. U	<b>Analysis of macronutrient and micronutrient intake with the incidence of stunting and wasting in toddlers 0-59 months of age at public health center in Bojong, Bogor regency, Indonesia</b>	<b>78</b>
Ginting. S. M. D Februhartanty. J Khusun. H	<b>Association between consumption of ultra-processed foods and beverages with nutritional status of private senior high school students in Pontianak, West Kalimantan, Indonesia</b>	<b>90</b>
Sutanto. L. B Winaktu, G. J. M. T Fabiani. H Muhardi. L	<b>Overview of fluid and macronutrient intake, knowledge and attitudes and eating behavior among private university medical students in Jakarta</b>	<b>104</b>

***Food and Nutrition: Functional Food***

Alverina A. C Susanto. M	<b>The role of polyphenols in atopic dermatitis: A literature review</b>	<b>111</b>
-----------------------------	--	------------



## EDITORIAL

### Nutritional care is a human right: incorporating principles into clinical practice

Gil Hardy

*Ipanema Research Trust, Auckland, New Zealand*

#### Introduction

The landmark Vienna Declaration (VD), initiated by the international human rights working group (IHRWG) and endorsed by more than 75 professional societies acknowledged that nutritional care is a human right alongside the right to food and the right to health. In a series of position papers the IHRWG have elaborated on the commitments required for translating human rights and ethical principles into clinical practice.<sup>1-3</sup> The ultimate objective of the VD is to ensure all patients have a right to be screened and diagnosed for disease related malnutrition (DRM) then to receive evidence based artificially administered nutrition and hydration (AANH) administered by an interdisciplinary team of experts to positively impact clinical outcomes and survival. Unfortunately, nutritional care in hospitals and post discharge is frequently below standard and is not part of the patient's holistic care.<sup>2</sup> Reasons include; inadequate education of healthcare professionals (HCPs), lack of malnutrition awareness, no reimbursement for nutrition treatments, or absence of public health policy.<sup>2,4</sup>

Ethics, that allow us to make decisions about what is right and wrong, and human rights are guiding values for clinical nutrition practitioners. Together they ensure a patient-centered approach, in which the needs and rights of the patients are of greatest importance.<sup>5</sup> An international human rights-based approach (HRBA) to clinical nutrition will encourage HCP to make evidence-based decisions in the best interests of their patient and can be articulated to a set of core values including

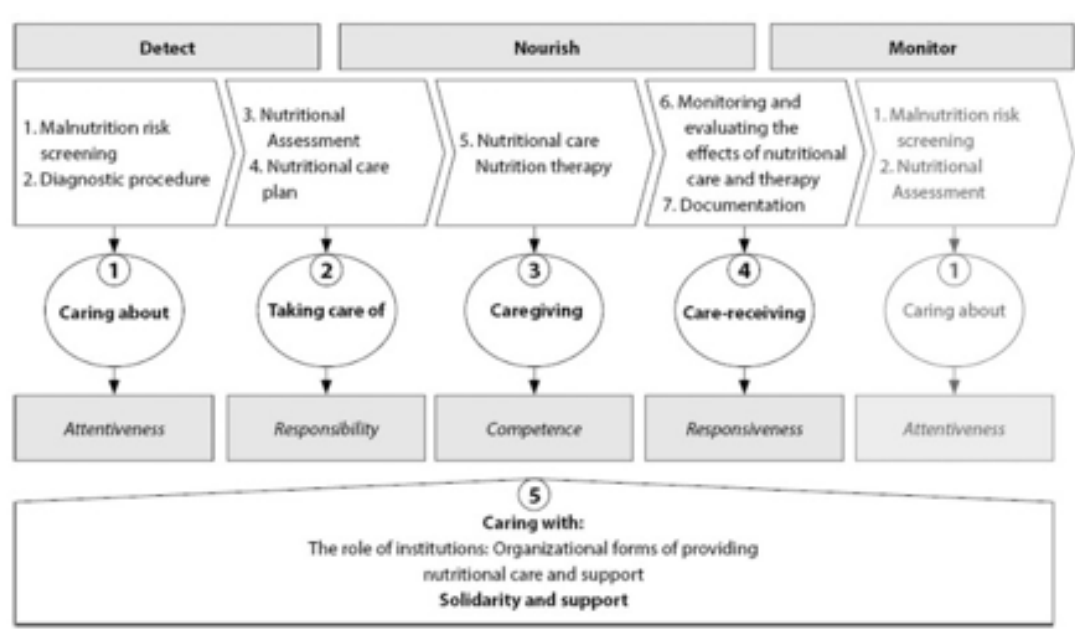
Fairness, Respect, Equality, Dignity and Autonomy. These five FREDA principles, when integrated into clinical nutrition guidelines and daily clinical practice, can inform decisions and optimise nutritional care.<sup>2</sup>

Comprehensive Nutritional care involves distinct, interrelated steps that should be provided ethically<sup>6</sup> in a systematic sequence<sup>7</sup> shown in Fig reproduced with permission from Cardenas et al.<sup>2</sup>

The "caring about" and "taking care of" phases of care require HCP to identify the need for nutritional care for those malnourished or at-risk of malnutrition, by using validated screening tools to assess patient's nutritional status.<sup>2</sup> A nutritional plan ensures all the nutritional requirements of the patient are addressed to combat malnutrition and improve quality of life.

In the third "caregiving" phase HCPs decide the best way provide nutrients orally, enterally, parenterally and/or by reinfusing the patients' own chyme. In this phase incompetence would result in the patients' needs not being met or in an increase in the risk of complications. Thus, HCPs must commit to life-long learning to ensure continuing competence in their practice.<sup>2</sup>

The success of nutritional therapy must be routinely monitored. The ethical element in the fourth "care receiving" phase is responsiveness to the way the patient/family/caregiver perceive their care.<sup>2</sup> Finally, the fifth, "caring with" phase defines policymakers, institutional managers and most importantly, the government as specific duty bearers with responsibilities to guarantee a HRBA.<sup>3</sup>



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In the third "caregiving" phase HCPs decide the best way provide nutrients orally, enterally, parenterally and/or by reinfusing the patients' own chyme. In this phase incompetence would result in the patients' needs not being met or in an increase in the risk of complications. Thus, HCPs must commit to life-long learning to ensure continuing competence in their practice.<sup>2</sup>

The success of nutritional therapy must be routinely monitored. The ethical element in the fourth "care receiving" phase is responsiveness to the way the patient/family/caregiver perceive their care.<sup>2</sup> Finally, the fifth, "caring with" phase defines policymakers, institutional managers and most importantly, the government as specific duty bearers with responsibilities to guarantee a HRBA.<sup>3</sup>

At the 2023 ASPEN conference the international clinical nutrition section proposed to create a national alliance that advocates and facilitates engagement with duty bearers. First to identify gaps then develop new policies and

institutional health procedures that address a HRBA to nutritional care. It was also proposed to create an expert advisory group (EAG), comprising strong advocates for a HRBA with experience in management of DRM. Other local experts with professional interests in HR/Ethics or familiarity with national government policy will enable the EAG to provide guidance for achieving the goals of the VD.<sup>9</sup>

## Conclusion

A global human rights-based approach to clinical nutrition involves treating patients with fairness, respect, equality, dignity and autonomy. Practical steps are advocated for developing and implementing national strategies and processes, endorsed by local institutions and policy makers, that ensure clinicians incorporate ethical and human rights values into their clinical practice for patients to receive optimum nutritional care.

## Conflict of interest

The authors declare that there is no conflict of interest related to the study.



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## CASE REPORT

## Effect of oral vitamin E supplementation on lipid profile in diabetes mellitus: evidence based case report

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### Abstract

**Introduction:** Diabetes mellitus, a prominent non-communicable disease, presents as a chronic condition associated with various complications, including heart disease, nerve damage, chronic kidney disease, and dyslipidemia. A pivotal abnormality in diabetic dyslipidemia is insulin resistance, which stimulates the production of Hepatic VLDL1 (very-low-density lipoprotein 1). The resulting overproduction of VLDL1 is metabolically linked to an abundance of small, dense LDL (low-density lipoprotein) particles and a reduction in large, cholesterol-rich HDL2 (high-density lipoprotein). Conversely, vitamin E, known for its antioxidant and anti-inflammatory properties, acts as a remover of peroxy radicals, preventing lipid oxidation and safeguarding polyunsaturated fatty acids (PUFA) within cells and plasma lipoproteins. **Method:** This study investigates the impact of oral vitamin E supplementation on the lipid profile in diabetic patients. Employing advanced search techniques on databases like PubMed, Cochrane Library, and Google Scholar, we conducted a comprehensive literature search using MeSH terms, advanced search methods, and specific eligibility criteria. The results yielded one systematic review with a meta-analysis and two randomized controlled trials (RCTs) that met the predefined PICO and eligibility criteria. **Results:** The systematic review and meta-analysis, along with one RCT, reported no significant reduction in lipid profiles with oral vitamin E supplementation in diabetic patients. In contrast, the other RCT observed an improvement in lipid profiles among diabetic patients receiving oral vitamin E supplementation. **Conclusion:** Supplementing with oral vitamin E does not enhance the lipid profile of individuals with diabetes mellitus.

**Keywords :** vitamin E, supplement, diabetes mellitus, lipid profile

### Case Scenario

A 62-year-old individual named Ms. LTE, who has been managing diabetes mellitus with a regular intake of 3x500 mg of metformin for the past seven years, was admitted to the hospital due to general weakness and reduced food intake. During her hospital stay, she underwent a series of laboratory tests, revealing elevated blood sugar levels (fasting blood glucose at 305 mg/dL) and dyslipidemia (with total cholesterol at 228 mg/dL, triglycerides at 197 mg/dL, HDL at 25 mg/dL, and LDL at 186 mg/dL). Upon the recommendation of an internal

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medicine specialist, Ms. LTE was referred to a clinical nutrition specialist for tailored nutrition therapy and education suitable for her condition. Additionally, the consultation aimed to explore the potential benefits of oral vitamin E supplementation in improving her lipid profile.

## Introduction

Diabetes mellitus is one of the four primary types of noncommunicable diseases characterized by its chronic nature and potential for causing severe harm to the body's systems.<sup>1</sup> As per the 2021 data from the International Diabetes Federation, approximately 537 million adults between the ages of 20 and 79 are currently dealing with diabetes on a global scale. It's noteworthy that more than three-quarters of these individuals reside in low to middle-income countries.<sup>2</sup> Individuals diagnosed with diabetes mellitus face a heightened risk, ranging from two to four times, of developing coronary artery disease (CAD), with CAD standing as the leading cause of mortality in the diabetic population. Dyslipidemia and hypertension represent significant controllable risk factors for diabetes mellitus and are closely linked to the occurrence of CAD. Furthermore, there is a notable association between metabolic syndrome, prediabetes, and diabetes mellitus, all of which elevate the risk of cardiovascular disease.<sup>3</sup>

According to clinical findings, dyslipidemia can lead to higher mortality rates in individuals with diabetes. It's often observed that diabetes patients commonly experience elevated triglyceride levels and reduced high-density lipoprotein (HDL-C) levels. Insulin resistance, a significant factor in diabetic dyslipidemia, plays a role in stimulating the production of Hepatic VLDL1. The liver primarily derives triglycerides (TG) from three major sources: 1) free fatty acids (FFA) originating from adipose tissue, 2) fatty acids derived from remnants of VLDL and chylomicron, and 3) De Novo Lipogenesis (DNL). The newly synthesized TG effectively inhibit the degradation of apoB within cells. In cases of insulin resistance, there is a diminished inhibition of hormone-sensitive lipase in adipose tissue, leading to an increased flow of FFA into the

portal system. The synthesis of TG from FFA, or even FFA itself, strongly hinders apoB degradation in the liver, consequently promoting the production of VLDL. In an insulin-resistant state, VLDL1 production is specifically amplified, with no significant effect on VLDL2 production. This overproduction of VLDL1 is metabolically linked to an abundance of small, dense LDL particles and a reduction in large, cholesterol-rich HDL2.<sup>4</sup> On the other hand, vitamin E, being a fat-soluble vitamin with antioxidant and anti-inflammatory properties, has been demonstrated to function as a remover of peroxy radicals, which aids in blocking the spread of free radicals and, as a result, prevents lipid oxidation. Within cells, vitamin E is present in the phospholipid layer of the cell membrane and in plasma lipoproteins, safeguarding polyunsaturated fatty acids (PUFA) from oxidation by peroxy radicals, that would have beneficial effects on lipid profile in a high-risk population such as diabetic patients.<sup>5,6</sup>

According to Khabaz et al.'s study,<sup>7</sup> vitamin E administration in diabetic patients was observed to lower triglycerides, total cholesterol, and LDL (low-density lipoprotein) levels. In contrast, another study by Mohammad et al.,<sup>8</sup> reported a contentious outcome regarding the impact of oral vitamin E supplementation for more than 12 weeks did not have a significant effect on lipid profiles in diabetic patients. However, a separate study by Aghadavod et al.,<sup>9</sup> revealed a significant reduction in total cholesterol and LDL levels as a result of oral vitamin E supplementation.

## Clinical question

P : Diabetes mellitus patients  
I : Oral vitamin E supplement  
C : Placebo  
O : Lipid profile

Clinical question: can administering vitamin E orally enhance the lipid profile of individuals suffering from diabetes mellitus?

## Methods

We conducted a comprehensive literature search on April 18, 2023, utilizing a combination of

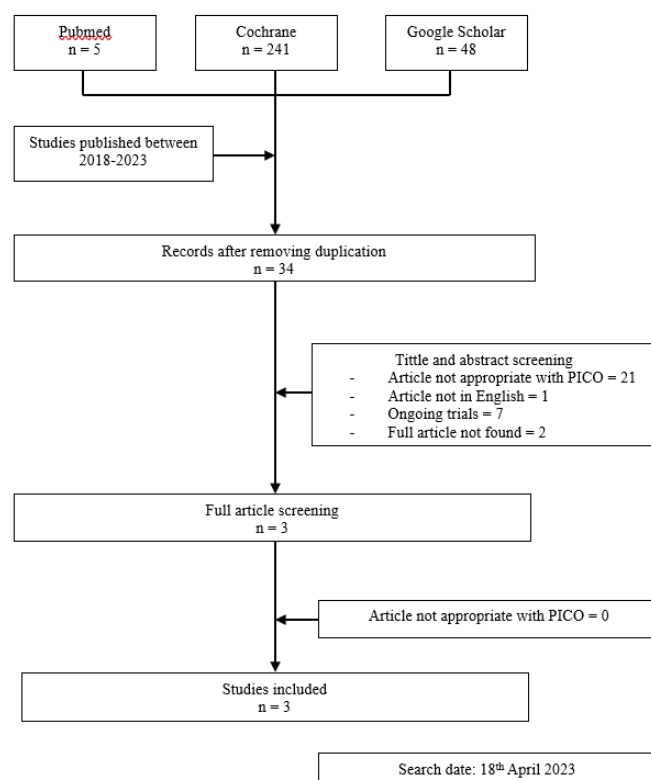
MeSH terms and Title/Abstract searches across three major databases: PubMed, the Cochrane Library, and an advanced search on Google Scholar. The keywords employed in the search included "vitamin E," "supplements," "diabetes mellitus," and "lipid profile." Our evaluation of the identified literature was guided by critical assessment tools and levels of evidence in accordance with the criteria established by the Oxford Center for Evidence-Based Medicine.

## Eligibility criteria

The inclusion criteria encompassed participants aged 18 years or older who had been diagnosed with diabetes mellitus, received oral vitamin E supplementation, and were part of a study designed as a randomized controlled trial (RCT), systematic review, or meta-analysis. These studies needed to report outcomes related to lipid profiles and have been published between 2018 and 2023, with the publication being in English. On the other hand, exclusion criteria consisted of animal studies, articles that were not accessible in full text, and studies in which participants received both intravenous and oral supplementation.

## Results

A visual representation in figure 1, in the form of a PRISMA flowchart, from the advanced search methods, Pubmed, Cochrane and Google Scholar, that published between 2018-2023, total obtained 294 journals, after removing duplications, title and abstract screening according to PICO, we got 3 studies included.



**Figure 1.** Prisma's Flow Chart

**Table 1.** Resources and Search Strategy

Database	Terminology	Hits	Eligible
PubMed	((oral vitamin E supplement) AND (diabetes mellitus)) AND (lipid profile)	5	1
Cochrane	#1 MeSH descriptor: [vitamin E] explode all trees #2 (vitamin E):ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Diabetes Mellitus] explode all trees #4 (lipid profile):ti,ab,kw (Word variations have been searched) #5 MeSH descriptor: [Administration, Oral] explode all trees #6 (oral):ti,ab,kw (Word variations have been searched) #7 #1 OR #2 #8 #3 OR #4 #9 #6 AND #7 AND #8	241	1
Google Scholar	allintitle: oral vitamin E diabetes mellitus lipid profile	48	1

In table 1, Pubmed search strategy using keywords: oral vitamin E supplement, diabetes mellitus, and lipid profile, obtained 5 journals and 1 eligible criteria. From Cochrane search strategy using MeSH descriptor vitamin E, diabetes mellitus, and oral, obtained 241 journals and 1 eligible criteria. From Google Scholar, using all in title: oral vitamin E diabetes mellitus lipid profile, obtained 48 journals and 1 eligible criteria.

**Table 2.** Study Characteristic

No	Author	Study design	Population characteristic	Total participants	Outcome	Key results
1	Mohammad, et al (2021) <sup>8</sup>	Systematic review and Meta-analysis RCT	Patients age 18–75 years old with diabetes mellitus who were given oral vitamin E supplementation 700 IU for 6-27 weeks.	613 (10 studies)	Lipid profile (TC, TG, HDL-C, and LDL-C)	Oral vitamin E supplementation ( $\alpha$ TF) did not have effect on TC (WMD: -0.69 mg/dl; 95% CI: -15.03, 13.65; p = 0.93), TG (WMD: 1.33 mg/dl; 95% CI: -9.19, 11.85; p = 0.80), HDL-C (WMD: 0.68 mg/dl; 95% CI: -1.25, 2.61; p = 0.51), and LDL-C (WMD: -0.52 mg/dl; 95% CI: -8.30, 7.25; p = 0.90) after supplementation >12 weeks
2	Aghadavod, et al (2018) <sup>9</sup>	RCT, double blind	Patients with diabetic nephropathy (DN) who were given oral vitamin E supplementation 800 IU for 12 weeks	54	Lipid profile (TC, TG, HDL-C, and LDL-C)	Oral vitamin E supplementation has significant reduction in TC (-14.3 $\pm$ 29.9 mg/dL versus -0.8 $\pm$ 13.1 mg/L, P = .03), LDL-C (-16.4 $\pm$ 28.5 mg/dL versus 0.1 $\pm$ 17.2 mg/L, P = .01), and TC-HDL-C ratio (-0.5 $\pm$ 0.7 versus 0.1 $\pm$ 0.5, P = .001)., LDL-C, and TC-HDL-C ratio
3	Dalan, et al (2020) <sup>10</sup>	RCT, double blind	Patients with diabetes mellitus who were given oral vitamin E supplementation 400 IU for 24 weeks	187	Lipid profile (TC, TG, HDL-C, and LDL-C)	Oral vitamin E supplementation did not have effect on TC and LDL-C when compared with placebo group.

RCT, randomized controlled trial; DN, diabetic nephropathy; TC, total cholesterol; TG, tryglicerides; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; WMD, weighted mean difference; CI, confidence interval.

**Table 3.** Validity Criteria

	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Mohammad, et al (2021) <sup>8</sup>	+	+	+	+	+	+	+	+	Moderate	1A-
Aghadavod, et al (2018) <sup>9</sup>	+	+	+	+	+	+	+	+	Moderate	1B
Dalan, et al (2020) <sup>10</sup>	+	+	+	+	+	+	+	+	Moderate	1B

\* Quality of evidence according to GRADE guidelines, <https://www.ncbi.nlm.nih.gov/pubmed/21208779>

\*\*Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), <http://www.cebm.net>.

+ clearly mentioned in the article; - not done? Not stated clearly

Systematic review and meta-analysis with troublesome heterogeneity

**Table 4.** Relevance Criteria

Article	Similarity Population	Similarity determinant/intervention/indicators	Similarity outcome
Mohammad, et al (2021) <sup>8</sup>	+	+	+
Aghadavod, et al (2018) <sup>9</sup>	+	+	+
Dalan, et al (2020) <sup>10</sup>	+	+	+

### Discussion

Diabetes mellitus (DM) is closely associated with an abnormal lipid profile. In DM, the primary features are insulin resistance (IR) and dysfunction of  $\beta$ -cells. Insulin resistance, a fundamental aspect of diabetic dyslipidemia, plays a pivotal role in stimulating the production of Hepatic VLDL1. The liver primarily acquires triglycerides (TG) from three major sources: 1) free fatty acids (FFA) originating in adipose tissue, 2) fatty acids derived from remnants of TRL (Very Low-Density Lipoprotein and chylomicron), and 3) De Novo Lipogenesis (DNL). The newly synthesized TG effectively block the degradation of apoB within cells. In cases of insulin resistance, there is a reduced inhibition of hormone-sensitive lipase in adipose tissue, resulting in an increased influx of FFA into the portal system. The synthesis of TG from FFA, or even FFA itself, strongly impedes apoB degradation in the liver, thereby promoting the production of VLDL.<sup>11</sup>

While remnants of TG-rich lipoprotein TRL and De Novo Lipogenesis (DNL) do contribute triglycerides (TG) to the liver, their role in inhibiting apoB degradation is relatively minor. Insulin resistance diminishes the breakdown of apoB, which is regulated by phosphoinositide (PI) 3-kinase, and it enhances the activity of microsomal triglyceride transfer protein (MTP), a key factor in VLDL assembly. In a state of insulin resistance, the production of VLDL1 is specifically increased, with minimal impact on VLDL2 production. This excessive VLDL1 production is associated with an abundance of small, dense LDL particles and a reduction in large, cholesterol-rich HDL2, linking it metabolically. A lipid profile assessment in diabetic patients may be useful to reduce the risk of disease progression and also for early intervention. Related to atherogenic dyslipidemia, coronary artery disease, and myocardial

infarction, diabetic patients have increased risk of cardiovascular disease (CVD).<sup>4,11,12</sup>

Vitamin E is composed of eight compounds, including  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherol, as well as  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocotrienols, all of which are lipid-soluble. Among these, the  $\alpha$ -forms of both tocopherols and tocotrienols are recognized as the most biologically active. However,  $\alpha$ -tocopherol is the most efficiently absorbed, with up to 90% entering the bloodstream and body tissues, while the other types of vitamin E are metabolized and excreted.<sup>13</sup> As per the Recommended Dietary Allowance (RDA), the suggested daily intake of vitamin E for individuals aged 14 years and older, regardless of gender, is 15 mg (equivalent to 22 international units, IU), and this recommendation remains consistent for diabetic patients as well as the general adult population. Vitamin E can be found naturally in specific foods like seeds, nuts, certain vegetables, and fortified products. Alternatively, vitamin E supplements are available. Vitamin E plays multiple roles in the body, with its primary function being that of an antioxidant, protecting cells from oxidative damage by counteracting harmful substances called free radicals. Additionally, it is vital for maintaining a robust immune system and facilitating cellular communication. Patients with diabetes mellitus often have compromised immune systems, making the supplementation of vitamin E essential for bolstering their immunity.<sup>14</sup>

Vitamin E, being a fat-soluble vitamin with antioxidant and anti-inflammatory properties, has been demonstrated to function as a remover of peroxy radicals, which aids in blocking the spread of free radicals and, as a result, prevents lipid oxidation. Within cells, vitamin E is present in the phospholipid layer of the cell membrane and in plasma lipoproteins, safeguarding polyunsaturated fatty acids (PUFA) from oxidation by peroxy radicals, consequently, vitamin E could potentially play a role in preventing or postponing the onset of chronic diseases linked to reactive oxygen species molecules.<sup>6</sup>

In a systematic review and meta-analysis conducted by Mohammad et al.,<sup>8</sup> it was reported

that the administration of oral vitamin E supplementation (specifically  $\alpha$ -tocopherol) did not demonstrate a significant impact on various lipid parameters, specifically total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), when the supplementation duration exceeded 12 weeks. The reported mean differences (WMD) and associated confidence intervals (95% CI) were as follows: TC (WMD: -0.69 mg/dl; 95% CI: -15.03, 13.65;  $p = 0.93$ ), TG (WMD: 1.33 mg/dl; 95% CI: -9.19, 11.85;  $p = 0.80$ ), HDL-C (WMD: 0.68 mg/dl; 95% CI: -1.25, 2.61;  $p = 0.51$ ), and LDL-C (WMD: -0.52 mg/dl; 95% CI: -8.30, 7.25;  $p = 0.90$ ). It is suggested that vitamin E supplements may modulate the proliferator-activated-receptor- $\gamma$  pathway, which activates genes related to fat synthesis and the differentiation of fat cells, leading to a reduction in cholesterol levels. Vitamin E is also believed to inhibit the signal protein kinase C pathway, which is associated with lipid metabolism. However, it's important to note some limitations of this study, including the sample sizes in certain included studies, a shortage of high-quality studies as assessed by the Jaded score, and the fact that the baseline vitamin E deficiency was not assessed in all the studies. This lack of assessment could potentially influence the results of the analyses.

The randomized controlled trial (RCT) conducted by Dalan et al.,<sup>10</sup> yielded a similar outcome, indicating that vitamin E supplementation had no discernible impact on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) when compared to the placebo group. This lack of effect may be attributed to the gene-dependent influence of vitamin E supplementation at the cellular level concerning the lipid profiles of diabetic patients. Notably, the study encompassed a diverse population comprising Chinese, Indian, and Malay ethnic groups, and it's conceivable that inherent disparities in lipid and metabolic profiles among these individuals may have contributed to the neutral results. Conversely, in a separate RCT led by Aghadavod et al.,<sup>9</sup> the findings demonstrated a significant reduction in TC ( $-14.3 \pm 29.9$  mg/dL compared to  $-0.8 \pm 13.1$  mg/L,  $P =$



.03), LDL-C ( $-16.4 \pm 28.5$  mg/dL compared to  $0.1 \pm 17.2$  mg/L,  $P = .01$ ), and the TC-HDL-C ratio ( $-0.5 \pm 0.7$  compared to  $0.1 \pm 0.5$ ,  $P = .001$ ) following vitamin E supplementation. The authors of this study concluded that high-dose vitamin E supplementation over a 12-week period had favorable effects on lipid profiles, except for triglycerides (TG) and very low-density lipoprotein cholesterol (VLDL-C). The inhibition of signal transduction pathways, including protein kinase C, is one way in which vitamin E intake may operate. Additionally, vitamin E supplementation may activate the proliferator-activated-receptor- $\gamma$  transduction pathway, subsequently leading to reduced cholesterol levels.

The study conducted by El-Aal et al.,<sup>15</sup> revealed significant alterations in metabolic markers following vitamin E supplementation, including improved glycemic control, increased levels of high-density lipoprotein cholesterol (HDL-C), and enhanced insulin function. Vitamin E was found to reduce lipid peroxidation and boost the activity of antioxidant enzymes in diabetic patients. In a systematic review and meta-analysis by Asbaghi et al.,<sup>16</sup> the combined intake of omega-3 and vitamin E was associated with a significant reduction in triglycerides (TG) (WMD:  $-28.34$  mg/dl, 95% CI:  $-37.44$ ,  $-19.22$ , with an I<sup>2</sup> of 59.6%) and low-density lipoprotein (LDL) (WMD:  $-8.07$  mg/dl, 95% CI:  $-15.10$ ,  $-1.05$ , with an I<sup>2</sup> of 90.9%). However, this combination did not have a significant impact on total cholesterol (TC) and high-density lipoprotein (HDL) (WMD:  $-11.48$  mg/dl, 95% CI:  $-24.15$ ,  $1.20$ , with an I<sup>2</sup> of 92.8%; WMD:  $-0.52$  mg/dl, 95% CI:  $-4.70$ ,  $3.66$ , with an I<sup>2</sup> of 95.5%), respectively. Vitamin E is a powerful antioxidant that dissolves in fat, and its insufficiency is associated with a range of illnesses. Increased levels of reactive oxygen species (ROSs) have been implicated in the development of metabolic syndrome. Therefore, maintaining adequate levels of vitamin E appears crucial in such

patients. Conversely, elevated ROSs lead to excessive lipid peroxidation, causing damage to proteins and DNA. Vitamin E, as a key component of the nonenzymatic antioxidative defense, mitigates damage to polyunsaturated fatty acids, such as omega-3 fatty acids. Consequently, numerous studies have explored the synergistic effects of these compounds.

However, the research by Al-Ramadhan et al.,<sup>5</sup> did not find any correlation between vitamin E and triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL). The authors attempted to explain the discrepancies in results from other studies, suggesting that differences in population and the specific forms of oral vitamin E supplements used might be contributing factors. Furthermore, they discussed the limited oral bioavailability of certain vitamin E forms, such as tocotrienols, which did not yield significant results in lipid profiles.

## Conclusions

Oral vitamin E supplements possess antioxidant and anti-inflammatory properties, making them a potential choice for reducing lipid profiles like total cholesterol and LDL in diabetic patients. However, after conducting critical reviews in this evidence-based case report, which included one systematic review and meta-analysis along with two randomized controlled trials (RCTs), it is evident that oral vitamin E supplementation does not lead to an improvement in the lipid profile of individuals with diabetes mellitus.

While the research did not demonstrate that vitamin E has a direct impact on reducing lipid profiles, it's worth noting that vitamin E can still be considered as a supplement for patients with chronic conditions such as diabetes mellitus. This is because it can help combat the increased presence of free radicals in the body due to the disease and serve as an antioxidant that supports overall immune system function.



## Conflict of interest

The authors declare that no conflict of interest with another person or institution.

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## CASE REPORT

### Effect of omega-3 supplementation on osteoarthritis: An evidence-based case report

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#### Abstract

**Background:** Osteoarthritis is marked by mild inflammation, causing cartilage damage that leads to bone remodelling and potentially reduces the quality of life. Omega-3 has anti-inflammatory properties, which can help mitigate cartilage damage.

**Objective:** This research aims to determine the role of omega-3 in relieving pain in patients with osteoarthritis.

**Methods:** A literature search was conducted using advanced searching on three large databases: PubMed, Cochrane, and Scopus. The search used Mesh terms according to the criteria. After assessing the relevance and suitability of the literature, two articles were selected and critically evaluated based on Oxford Center for Evidence-Based Medicine.

**Results:** Two systematic review-meta-analyses that meet the PICO and eligibility criteria were found. One of the literature sources does not demonstrate the effect of omega-3 supplementation on joint pain, while the other literature source shows the beneficial effects of omega-3 in reducing joint pain in osteoarthritis.

**Conclusion:** Omega-3 supplementation can alleviate joint pain in individuals with osteoarthritis. Providing omega-3 may be worth considering.

**Keywords:** omega-3, osteoarthritis, joint pain

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## Case scenario

A 56-year-old woman came to the nutrition clinic for consultation. The patient is actively working and has been suffering from osteoarthritis for the past 5 years. Her complaints include stiffness and pain in the hands and knees, along with occasional cracking sounds during certain movements. She also experiences frequent muscle fatigue in the neck and waist area. The patient is currently taking Arcoxia 60 mg once daily, Myonal 50 mg twice daily, and Neurobion 1 tablet once daily. She is overweight and frequently consumes fast food. The patient wants to start a healthy diet and exercise routine. She inquires if taking omega-3 supplements can help reduce the joint pain she is experiencing?

## Introduction

Musculoskeletal health encompasses bones, cartilage, tendons, ligaments, muscles, and connective tissues. Balanced metabolism is crucial for maintaining musculoskeletal system homeostasis. Osteoarthritis (OA) is one of the common musculoskeletal disorders, with a global prevalence of 15%, projected to reach 35% by 2030.<sup>1</sup> Currently, there are 303 million people worldwide suffering from osteoarthritis.<sup>2</sup> The estimated number of osteoarthritis patients in the United States will reach 78 million by 2040.<sup>3</sup> The prevalence of joint diseases is around 7.3% in Indonesia.<sup>4</sup>

Osteoarthritis is a degenerative joint disease characterized by the damage to cartilage tissue, ligaments, synovial inflammation, osteophyte formation, and bone remodeling.<sup>1</sup> This condition is caused by low-grade inflammation, which subsequently disrupts the homeostasis of cartilage synthesis and degradation.<sup>5</sup> Osteoarthritis commonly affects the hands, hips, and knees, gradually leading to cartilage deterioration and bone changes, resulting in pain, stiffness, and swelling, which can lead to decreased function and disability.<sup>6</sup> Osteoarthritis patients are susceptible to experiencing depression, memory loss, and even suicidal thoughts.<sup>7</sup> Risk factors include being above 50 years of age, genetics, female gender,

bone or joint structural disorders, joint injuries, muscle weakness, obesity, physical activity, and diet.<sup>6,8</sup>

Assessment of OA diagnosis relies on clinical symptoms and physical examination. If OA is suspected, it is important to conduct a medical history, perform a physical examination, and employ an approach to rule out other possible diagnoses, along with using supplementary tests. Basic radiological examinations can help confirm the presence of OA and exclude other conditions.<sup>6,8</sup> Preventing osteoarthritis can be achieved by adopting a healthy lifestyle and avoiding injuries. This includes maintaining a balanced and nutritious diet, engaging in at least 150 minutes of physical activity per week, practicing good body posture, and managing weight if there is excess or obesity.

The development of OA involves various pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-8, and signaling pathways such as nuclear factor kappa B (NF- $\kappa$ B), protein kinase B (Akt), c-Jun N-terminal kinases (JNK), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 6 (STAT6), and mammalian target of rapamycin (mTOR). These cytokines and signaling pathways can increase chondrocyte catabolism and inhibit anabolism, leading to disruptions in homeostasis and cartilage degradation.<sup>9</sup>

The fat present within articular cartilage chondrocytes can trigger inflammation, chondrocyte damage, and cartilage degradation. Omega-6 fatty acids are pro-inflammatory and accumulate in osteoarthritis joints. Conversely, omega-3 fatty acids are anti-inflammatory and are inversely related to patellofemoral cartilage damage.<sup>10</sup> Omega-3 includes  $\alpha$ -linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). While  $\alpha$ -linolenic acid can be converted into EPA/DHA, the amount is not significant. Through elongation and saturation processes, EPA and DHA will produce anti-inflammatory eicosanoids such as prostaglandin (PG3), leukotrienes (LTB5), thromboxane (TXA3), and resolvins (RvE1, RvE2, RvD3, RvD4). These substances can reduce pain in osteoarthritis by decreasing the production of pro-inflammatory eicosanoids, reactive oxygen

species, cytokines, and through the mediation of anti-inflammatory agents.<sup>11</sup>

Some studies have shown that the administration of omega-3 can reduce the symptoms of pain in osteoarthritis. The purpose of conducting the EBCR (Evidence-Based Case Report) is to conduct a thorough examination of the effects of administering omega-3 on pain in osteoarthritis, considering all available evidence and data to make informed and evidence-based.

## Clinical question

P : osteoarthritis patient

I : omega-3 supplement

C : placebo

O : joint pain

Clinical question: could omega-3 supplementation reduce joint pain?

## Methods

Literature search was conducted using PubMed, Cochrane, and Scopus databases on June 4, 2023. MeSH terms, title/abstract/keywords were used for the database search. The keywords used were 'osteoarthritis' AND 'omega-3 fatty acid' OR 'omega 3 eicosapentaenoic acid' AND 'joint pain' (**Table 1**) to investigate the role of omega-3 in alleviating pain in individuals with osteoarthritis. After obtaining the results from these databases, title and abstract screening were performed, followed by selection based on inclusion criteria, and checked for duplications. Literature relevant to the PICO (Population, Intervention, Comparison, Outcome) was filtered using criteria for full-text and English language. Critical appraisal of the included studies was carried out following the systematic review guidelines published by the University of Oxford Centre for Evidence-Based Medicine (CEBM).

## Eligibility criteria

Inclusion criteria for the study were as follows:

1. Age  $\geq$  18 years.
2. Subjects diagnosed with osteoarthritis.
3. Intervention involving omega-3 fatty acids.
4. Study design: systematic review–meta analysis or randomized controlled trial (RCT).
5. Articles published within the last 10 years.
6. Articles published in the English language.

Exclusion criteria:

1. Subjects undergoing analgesic therapy.
2. Studies conducted on animals.
3. Studies with outcomes that do not assess joint pain.

## Results

There are 76 literatures from Pubmed, 4 literatures from Cochrane, and 60 literatures from Scopus (**Table 1**). The literature was sorted using a search engine filter, which screened titles and abstracts based on inclusion criteria and removed duplicates. After reading the full texts, we utilized two literatures from systematic reviews and meta-analyses. The literature originates from Senfleber et al.<sup>12</sup> and Deng et al.<sup>13</sup> The flowchart of the search and selection strategy can be seen in **Figure 1**. The characteristics of the literature are presented in **Table 2**. The description of the eligible criteria can be found in **Table 3**.

## Discussion

Joint pain is one of the common complaints found in osteoarthritis patients, which can cause disability and reduce long-term quality of life. The administration of omega-3 with EPA and DHA content has anti-inflammatory properties that can reduce the expression of proinflammatory genes associated with cartilage degradation.

There are two systematic reviews and meta-analyses of randomized controlled trials that can be used to address the clinical question. Senfleber et al.<sup>12</sup> compared the administration of omega-3 with placebo in subjects with osteoarthritis, rheumatoid arthritis, or mixed arthritis, focusing on joint pain,

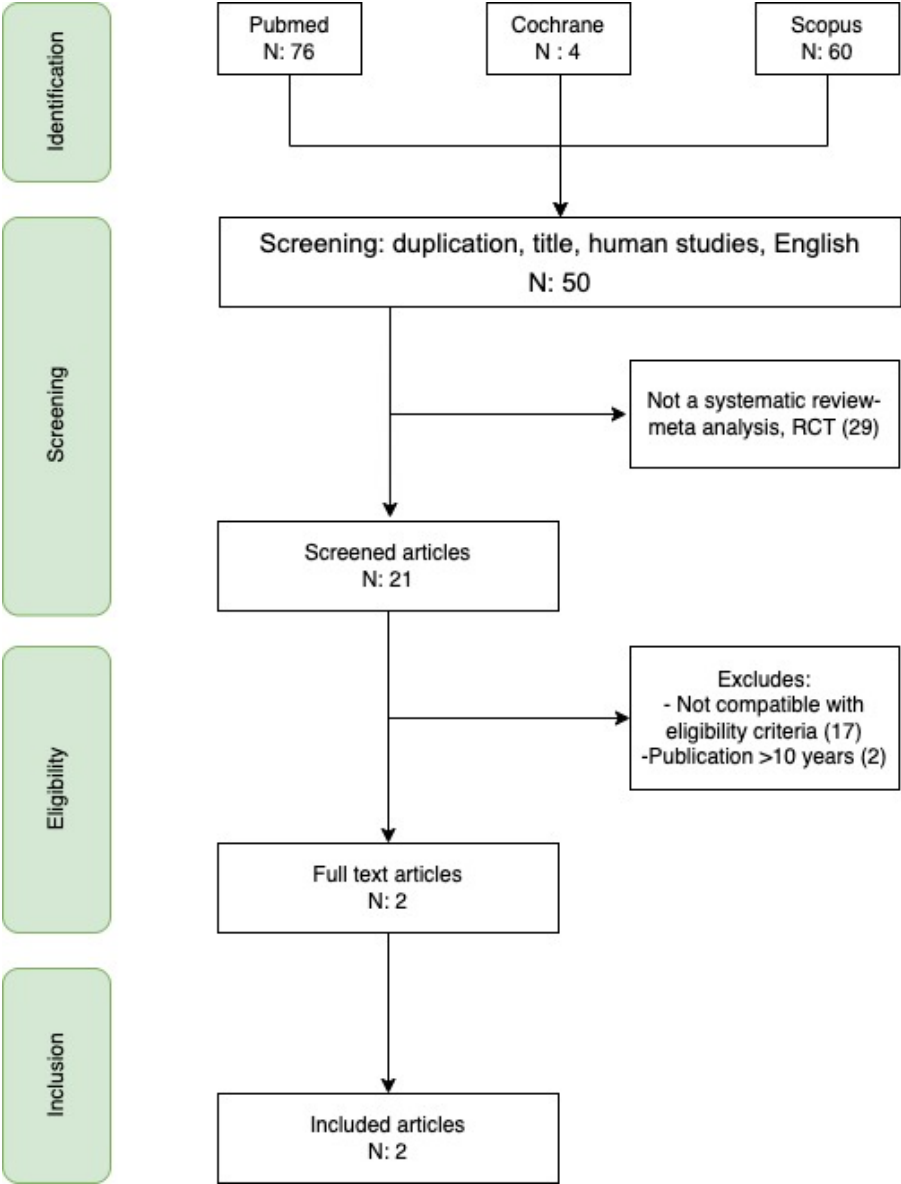
function, and inflammation. The intervention involved the oral administration of marine oil containing omega-3 to reduce arthritis pain. The marine oil used in the studies included fish oil, cod liver oil, shellfish extract, krill oil, and seal oil. The results of the studies showed an effect of marine oil on joint pain. However, there was high heterogeneity in the studies ( $I^2 = 63\%$ ) due to variations in diagnosis, types, and dosage of supplementation. Only 5 out of 42 studies assessed the effect of marine oil on patients with osteoarthritis. The studies indicated no effect on OA patients given EPA and DHA. Conversely, there was a significant effect in the rheumatoid arthritis and mixed arthritis groups, with an 8%

improvement on the visual analogue scale (VAS). The funnel plot and Egger's test results indicated low publication bias. The sensitivity analysis using the fixed-effect model showed no small study bias.

A recent study by Deng et al.<sup>13</sup> showed that the administration of omega-3 significantly reduces joint pain compared to placebo in patients with osteoarthritis (standardized mean difference (SMD):  $-0.29$ , 95% confidence interval (CI)  $-0.47$  to  $-0.11$ ,  $p = 0.002$ ,  $I^2 = 60\%$ ). The assessment of joint pain used the Western Ontario-McMaster University Osteoarthritis Index (WOMAC) and Visual Analog Scale (VAS). This study analyzed OA patients given omega-3 ranging from 350 to 2400 mg. There was high heterogeneity in this study (Cochrane Q test = 0.01,  $I^2 = 60\%$ ).

**Table 1.** Search strategy

Database	Search Strategy	Hits
Pubmed	(((osteoarthritis[MeSH Terms]) AND (fatty acids, omega 3[MeSH Terms])) OR (omega 3 eicosapentaenoic acid[MeSH Terms])) AND (pain[Title/Abstract])	76
Cochrane	#1 MeSH descriptor: [Osteoarthritis] explode all trees #2 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees #3 (joint pain):ti,ab,kw #4 #1 AND #2 AND #3	4
Scopus	( TITLE-ABS-KEY ( osteoarthritis ) AND TITLE-ABS-KEY ( omega 3 fatty AND acid ) AND TITLE-ABS-KEY ( joint AND pain ) )	60



**Figure 1.** Prisma flow chart



**Table 2.** Study characteristic

Articles	Study Design	Population	Outcome	Result
Senftleber et al. <sup>12</sup> (2017)	Systematic review and Meta-analysis of Randomized Controlled Trials	42 studies involving 2,751 patients. These studies compared the administration of marine oil in patients with arthritis, with a minimum duration of 2 weeks of treatment. Among these, 32 studies examined rheumatoid arthritis, 6 studies examined osteoarthritis, and 4 studies examined mixed arthritis.	Joint pain was assessed using the Visual Analog Scale (VAS), inflammation was measured using C-reactive protein (CRP), and joint function was evaluated through walking tests and grip strength assessments.	There is a slight effect of marine oil in reducing joint pain in arthritis patients (SMD -0.24; 95% CI, -0.42 to -0.07; heterogeneity $I^2 = 63\%$ ). However, there is no significant effect on osteoarthritis patients (SMD -0.17; 95% CI, -0.57 to 0.24).
Deng et al. <sup>13</sup> (2023)	Systematic review and Meta-analysis of Randomized Controlled Trials	There are 9 studies involving 2,070 patients with osteoarthritis. These studies compared the administration of omega-3 with placebo regarding the reduction of joint pain.	Joint pain and function were evaluated using the Western Ontario-McMaster University Osteoarthritis Index (WOMAC) or Visual Analog Scale (VAS).	Omega-3 supplementation significantly reduces pain compared to placebo (SMD: -0.29, 95% CI -0.47 to -0.11, $p = 0.002$ ). Subgroup analysis showed consistent pain improvement evaluated by WOMAC or VAS after n-3 PUFA supplementation, regardless of whether the dose was less than or equal to 1000 g/day, with EPA < 500 mg/day or $\geq 500$ mg/day, and with DHA < 500 mg/day or $\geq 500$ mg/day. The study also found an improvement in joint function with omega-3 supplementation (SMD: -0.21, 95% CI -0.34 to -0.07, $p = 0.002$ , $I^2 = 27\%$ ).



**Table 3.** Validity criteria

	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Senftleber et al. <sup>12</sup>	+	+	+	+	+	+	+	+	Moderate	1A-
Deng et al. <sup>13</sup>	+	+	+	+	+	+	+	+	Moderate-High	1A-

\* Quality of evidence according to GRADE guidelines, <https://www.ncbi.nlm.nih.gov/pubmed/21208779>  
\*\*Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), <http://www.cebm.net>.  
+ clearly mentioned in the article; - not done; ? Not stated clearly  
- Systematic review and meta-analysis with heterogeneity

**Table 4.** Criteria relevance

	Similarity Population	Similarity Intervention	Similarity Outcome
Senftleber et al. <sup>12</sup>	+	+	+
Deng et al. <sup>13</sup>	+	+	+

However, subgroup analysis found consistent reduction in joint pain with the administration of omega-3 PUFA, regardless of whether the dose was less than or equal to 1000 g/day, with EPA < 500 mg/day or ≥ 500 mg/day, and with DHA < 500 mg/day or ≥ 500 mg/day. The study also found an improvement in joint function with omega-3 supplementation (SMD: -0.21, 95% CI -0.34 to -0.07,  $p = 0.002$ ,  $I^2 = 27\%$ ). The results of the funnel plots and Egger's regression test indicate that this study has a low risk of publication bias. This further strengthens the potential of omega-3 in reducing joint pain.

The role of omega-3 in reducing joint pain occurs through its anti-inflammatory properties. Omega-3 produces anti-inflammatory eicosanoids, such as prostaglandins, leukotrienes, thromboxanes, and resolvins, which suppress inflammation, catabolic responses, and reduce chondrocyte apoptosis.<sup>14</sup> A study by Chen et al.<sup>15</sup> found that DHA acts as an agonist for G-protein-

coupled receptor 120 (GPR120), which plays a role in homeostasis and regulation of free fatty acids, as well as inflammation prevention. Patients with OA have lower levels of GPR120, and patients given DHA showed reduced expression of proinflammatory genes. Additionally, the metabolite of DHA, called maresin-1, contributes to cartilage damage reduction and an increase in collagen in cartilage.<sup>16</sup> These findings further strengthen the benefits of omega-3 in reducing inflammation and pain in OA patients.

Omega-3 is obtained from foods such as salmon, tuna, mackerel, cereal, walnuts, flaxseeds, and grains.<sup>17</sup> Currently, there are also omega-3 supplementation forms (fish oil) available, which can enhance the effects of anticoagulant and antidepressant medications, but may also cause stomach discomfort.<sup>18</sup> Consuming a diet rich in omega-3 will influence the composition of fatty acids in cell membranes that can alter signaling and gene expression, leading to anti-inflammatory

effects, reduced catabolic responses, and decreased chondrocyte apoptosis.

Based on the two literatures mentioned above, there are conflicting results regarding the administration of omega-3 on reducing joint pain in patients with osteoarthritis. This discrepancy may be due to the limited number of osteoarthritis studies in Senfleber et al.'s research. On the other hand, the more specific study conducted by Deng et al., which focused on patients with osteoarthritis, showed a significant reduction in joint pain. Consistent results were also obtained in subgroup analysis. This further strengthens the benefits of omega-3 in reducing inflammation and pain in OA patients.

## Conclusion

Based on the critical review conducted on two systematic reviews and meta-analyses, it can be concluded that the supplementation of omega-3 can still provide benefits to patients with osteoarthritis. Omega-3 can be administered either through dietary sources or supplements.

## Conflict of interest

Authors declared no conflict of interest regarding this article.

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## The correlation of folic acid and homocysteine serum with vascular density and retinal non-perfusion area in diabetic retinopathy

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### Abstract

**Background :** Diabetic Retinopathy (DR) is the most common microvascular complication of Diabetes Mellitus (DM). Homocysteine has been studied as a biomarker in DR, while folic acid exhibits anti-proliferative effects in DR.

**Objective :** To analyze the correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion area in healthy individuals and patients with diabetic retinopathy.

**Methods :** This is an observational study with a cross-sectional design, conducted in Dr. Kariadi Hospital and GAKI laboratory in Semarang in January 2023. This study included 60 samples: 15 healthy individuals, 15 patients with DM but no DR, 15 patients with Non-Proliferative Diabetic Retinopathy (NPDR), and 15 patients with Proliferative Diabetic Retinopathy (PDR). Patients were examined for serum folic acid and homocysteine using blood laboratory tests, vessel density and retinal non-perfusion areas using optical coherence tomography angiography (OCTA).

**Results :** There was a negative correlation with weak strength between folic acid levels and retinal non-perfusion area of the retina in all samples (Folic acid levels vs retinal non-perfusion area,  $p = 0.009$ , Spearman correlation =  $-0.335$ ). There was a positive correlation with weak strength between folic acid levels and vascular density in all samples (Folic acid levels vs vascular density,  $p = 0.009$ , Spearman correlation =  $0.337$ ). There was a positive correlation with moderate strength between homocysteine levels and retinal non-perfusion area in all samples (Homocysteine levels vs non-perfusion area of the retina,  $p = 0.001$ , Spearman correlation =  $0.426$ ). There was a positive correlation with moderate strength between homocysteine levels and vascular density in all samples (Homocysteine levels vs vascular density,  $p = 0.001$ , Spearman correlation =  $-0.414$ ).

**Conclusion :** There was a correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion areas.

**Keywords:** Folic acid, Homocysteine, Vascular density, retinal non-perfusion area, Diabetic Retinopathy

### Introduction

Diabetic retinopathy (DR), a major microvascular complication of Diabetes Mellitus (DM), poses a

significant risk of sight-threatening retinal damage. It is one of the leading causes of blindness in adults.<sup>1-5</sup> According to The Early Treatment Diabetic Retinopathy Study (ETDRS), DR is categorized into Non-proliferative (NPDR) and Proliferative (PDR) types, diagnosed through vascular abnormalities in the retina.<sup>6</sup> Often undetected, the study on the prevalence of DR in Indonesia reports that among Indonesian adults

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with type 2 diabetes in urban and rural areas, around 1 in 4 adults with diabetes suffers from vision-threatening DR.<sup>5</sup> It was reported in 2020 on the global prevalence of DR study that the number of adults worldwide with DR and vision-threatening DR was estimated at 103.12 million and 28.54 million respectively. These numbers were projected to increase to 160.50 million and 44.82 million, respectively.<sup>4</sup> This highlights the urgent need for effective DR screening, prevention and therapy methods.

In Diabetes Mellitus, Hyperglycemia initiates alternate pathways for metabolizing glucose. These pathways lead to the release of cytokines and growth factors, resulting in vascular endothelial impairment, increased vascular permeability, and microvascular occlusion. This occlusion subsequently causes retinal ischemia.<sup>7,8</sup> Retinal non-perfusion areas are quantitative biomarkers to characterize ischemia in DR.<sup>7,9</sup> Inflammatory cytokines and growth factors released in response to hyperglycemia can exacerbate endothelial damage and pericyte loss.<sup>7,10</sup> Endothelial cell damage can result in capillary dropout, a key feature leading to reduced vascular density without pericyte support. Capillaries become destabilized and may collapse, leading to a decrease in vascular density.<sup>11,12</sup> Optical coherence tomography angiography (OCTA) allows visualization of retinal capillaries and measures retinal non-perfusion areas.<sup>9</sup>

Folic acid, also known as vitamin B9, is an essential water-soluble vitamin for human health. It is a synthetic form of folate, a naturally occurring B vitamin found in certain foods.<sup>13</sup> The research conducted by Zhenglin Wang et al.<sup>14</sup> showed that folic acid could suppress the proliferation of retinal vascular endothelial cells (RVECs) by 33.33%. Therefore, these findings suggested that folic acid has an inhibitory effect on the proliferation and migration of endothelial or vascular smooth muscle cells (VSMC).<sup>14</sup> Research by Vviviek Dave, et al.<sup>15</sup> showed that Folic acid plays a protective role against retinal thinning in the early stages of DR in mice genetic model of type 2 diabetes mellitus obesity. These findings suggested that Folic acid may serve as a

potential therapeutic agent against DR through potential suppression of angiogenesis, inflammation, and oxidative stress.<sup>15</sup> Homocysteine has been investigated as a biomarker as well as a risk factor for vascular disease. Homocysteine is involved in oxidation-reduction reactions and induces oxidative stress.<sup>16</sup> Xunwen Le et al.<sup>17</sup> conducted a meta-analysis study summarized studies involving a total of 2.184 diabetic patients and found elevated homocysteine levels associated with an increased risk of DR in patients with Diabetes Mellitus.<sup>17</sup> Several studies have shown an association between folic acid and homocysteine with vascular disease, especially in DR with various underlying mechanisms. Meanwhile, research into how folic acid and homocysteine serum affect vascular density and retinal non-perfusion areas has never been studied.<sup>13-17</sup> Given the accessibility and cost-effectiveness of serum folic acid and homocysteine testing, as well as folic acid supplementation or dietary interventions, these factors hold promise as potential therapeutic or preventive agents in DR management. They may also serve as preliminary diagnostic tools for DR identification. This study aims to determine the correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion area.

## Methods

This study was an observational study with a cross-sectional design. Sample size uses measures for unpaired numerical, analytical comparisons. The sample size was determined based on statistical calculations by setting a confidence level of 95% and a power test of 95%; thus, the results of the formula for calculating the minimum sample used were 60 samples. The total sample of this study was 60 patients. The samples were 15 healthy patients, 15 diabetes mellitus patients without diabetic retinopathy (DM), 15 patients with non-proliferative type diabetic retinopathy (NPDR), and 15 patients with proliferative type diabetic retinopathy (PDR) who came to the Merpati eye clinic of Dr. Kariadi Hospital Semarang.



This study was conducted in Dr. Kariadi Hospital and GAKI laboratory in Semarang in January 2023. Patients were examined for serum folic acid and homocysteine using blood laboratory tests. Vessel density and retinal non-perfusion areas were examined using optical coherence tomography angiography (OCTA). Optical Coherence Tomography (OCT) is a non-invasive imaging technology that can detect loss of retinal nerve tissue by qualitatively assessing the retinal layers and quantitatively measuring the thickness of the retinal tissue with high resolution.<sup>18</sup> Optical Coherence Tomography Angiography (OCT-A) can non-invasively map ocular blood flow circulation to the capillary stage, relate perfusion to neuronal damage, describe microvascular and neuronal connections in DM, and find one of the predictive markers for diabetic retinopathy.<sup>19,20</sup> From the results of the OCTA scan image, a trained ophthalmologist assesses the distribution and pattern of blood vessels. This assessment can help identify areas of abnormal or reduced blood flow. Vascular density is obtained from the proportion of the scan area occupied by blood vessels. This is represented as a percentage. The ophthalmologist also manually examines the OCTA images to identify and confirm areas of non-perfusion. These areas may appear as dark or empty spaces in the blood vessel tissue.

Inclusion criteria were patients with a history of DM, funduscopy examination found with diabetic retinopathy or without diabetic retinopathy by ETDRS, and for healthy patients there was no history of DM or signs of DR. The exclusion criteria for this study were patients who had undergone lasers, anti-VEGF injections, and vitrectomy surgery. Analysis was carried out to determine the differences in folic acid levels, homocysteine serum levels, vascular density, retinal non-perfusion area between groups, and the correlation between folic acid and homocysteine with vascular density and non-perfusion area of the retina in all samples. The data in this study were analyzed using SPSS 26. For comparing all groups, the One-Way ANOVA test or the Kruskal-Wallis test was used, while the comparison between two groups was conducted

using the Mann-Whitney test. The One Way ANOVA test was used to compare more than two groups, and in this study, it was used for comparing four groups. Following a significant ANOVA result, the Games-Howell test served as a post-hoc analysis to identify the specific groups that differ. The correlation test was used to determine the correlation between folic acid and homocysteine serum with vascular density and retinal non-perfusion area in all samples.

This research was approved by the Health Research Ethics Commission of the Faculty of Medicine, Diponegoro University / Dr. Kariadi Central General Hospital Semarang no.1349/EC/KEPK-RSDK/2022 and research permit number: DP.02.01/I.II/10484/2022.

## Results

This study analyzed a total of 60 samples: 15 from healthy patients (without DM), 15 samples of patients with Diabetes mellitus (DM) without DR, 15 samples of DM patients with non-proliferative diabetic retinopathy (NPDR), and 15 samples of DM patients with proliferative diabetic retinopathy (PDR).

**Table 1.** Sample characteristics

Age (years)		
Mean	46.63 ± 11.88	
Median	50.00	
Modus	52	
minimum	23	
maximum	67	
Gender	Frequency	Percentage
Female	39	65 %
Male	21	35 %
Total	60	100 %

Patients' average age was 46.63 ± 11.88 years. Patients' sex were predominately female (65%) while men were only 21%.

**Table 2.** The comparison of each variable in all sample groups

Variable	Groups	Mean $\pm$ SD	p
<b>Folic Acid (ng/ml)</b>	Healthy patients (n=15)	5.62 $\pm$ 2.25	0.055
	DM (n=15)	6.05 $\pm$ 3.83	
	NPDR (n=15)	4.74 $\pm$ 0.56	
	PDR (n=15)	4.72 $\pm$ 0.59	
<b>Homocystein Serum (<math>\mu</math>mol/L)</b>	Healthy patients (n=15)	4.38 $\pm$ 2.22	0.008*
	DM (n=15)	7.28 $\pm$ 3.24	
	NPDR (n=15)	7.50 $\pm$ 3.63	
	PDR (n=15)	8.50 $\pm$ 3.85	
<b>Vascular Density (mm/mm<sup>2</sup>)</b>	Healthy patients (n=15)	18.82 $\pm$ 0.42	0.000*
	DM (n=15)	17.37 $\pm$ 0.59	
	NPDR (n=15)	15.85 $\pm$ 0.51	
	PDR (n=15)	13.33 $\pm$ 1.36	
<b>Retinal non- perfusion areas (%)</b>	Healthy patients (n=15)	53.41 $\pm$ 0.94	0.000*
	DM (n=15)	57.30 $\pm$ 1.18	
	NPDR (n=15)	60.29 $\pm$ 1.07	
	PDR (n=15)	67.29 $\pm$ 3.91	

Note : \* significant ( $p < 0.05$ )

The folic acid difference test was performed using the Kruskal Wallis test because the folic acid level data was abnormally distributed based on the normality test. There are no significant differences in folic acid levels between all the case groups ( $p = 0.055$ ). One-Way Anova test was done to analyze serum homocysteine levels, vascular density, and retinal non-perfusion area because the data was normally distributed. From the results of the Homocysteine difference test, Homocysteine based on the case group showed significant differences ( $p = 0.008$ ). The results of the vascular density and retinal non-perfusion area difference test based on case groups also showed significant differences ( $p < 0.01$ ).

Post hoc Games-Howell test was conducted to determine the difference in homocysteine serum, vascular density, and retinal non-perfusion area between groups. Meanwhile, folic acid levels did not proceed to the post hoc test because there was no significant difference in the difference test between all groups. In the Games-Howell Post

hoc test, significant differences were found in serum homocysteine levels between healthy groups with DM groups ( $p=0.041$ ), NPDR (0.043) and PDR groups (0.008). There were significant differences between the entire group in vascular density and retinal non-perfusion areas.

**Table 3.** The comparison of folic acid levels between patients without DR and with DR

Group	Mean $\pm$ SD (ng/ml)	p
<b>Patients Without DR (n=30)</b>	5.84 $\pm$ 3.10	0.011*
<b>Patients With DR (n=30)</b>	4.74 $\pm$ 0.57	

Because there was no significant difference in the Kruskal Wallis test, an analysis was carried out to determine the comparison of folic acid levels between patients without DR (healthy patients and DM patients without DR) (n=30) and the group of patients with DR (patients with



**Table 4.** Correlation test results of homocysteine and folic acid with retinal non-perfusion areas and vascular density in all samples

		Retinal non-perfusion areas	Vascular Density
Homocystein Serum	<i>r</i>	0.426	-0.414
	<i>p</i>	0.001*	0.001*
Folic Acid	<i>r</i>	-0.335	0.337
	<i>p</i>	0.009*	0.009*

NPDR and PDR) (n=30). The Mann-Whitney test to determine the comparison of folic acid levels in patients with DR and without DR, obtained significant differences in the group of patients without DR and the group of patients with DR (p = 0.011)

The Spearman correlation test was also conducted to determine the correlation between folic acid and homocysteine serum with vascular density and non-perfusion area retina in all samples (n=60). The correlation value of homocysteine and the non-perfusion area was p = 0.001 with a Spearman correlation value of 0.426, showing a positive correlation with moderate correlation strength. In the correlation between homocysteine and vascular density, a value of p = 0.001 was obtained with a Spearman correlation value of -0.414, showing a negative correlation with moderate correlation strength. In the correlation between folic acid and non-perfusion areas, a value of p = 0.009 with a Spearman correlation value of -0.335 showed a negative correlation with weak correlation strength. In the correlation between folic acid and vascular density, a value of p = 0.009 was obtained with a Spearman correlation value of 0.337, showing a positive correlation with a weak correlation strength.

**Discussion**

This study revealed significant correlations between folic acid and homocysteine levels with retinal conditions in all samples. A negative correlation with weak strength was found

between folic acid levels and retinal non-perfusion area, suggesting that higher folic acid levels are associated with reduced non-perfusion area in the retina. Conversely, a significant but weak positive correlation was observed between folic acid levels and vascular density, indicating that higher folic acid levels are associated with increased vascular density in the retina. Previous research by Liu X et al.<sup>21</sup> on the palliative effects of folic acid on microvessels in the retina in diabetic retinopathy explained that the source of expression and the epigenetic profile within retinal microvascular endothelial cells, emphasizing the pharmacological mechanism of folic acid on DNA methylation and hydroxymethylation regulation within microvessel cells in DR.<sup>21</sup> Folic acid can downregulate a panel of genes associated with angiogenesis, inflammation, and oxidative stress.<sup>15</sup> In this study, a comparison of folic acid levels based on the 4 case groups (PDR, NPDR, DM no DR, and healthy patients) showed no significant difference. However, there was a significant difference in folic acid levels between patients without DR (healthy patients and DM patients without DR) compared with those with DR (Patients with NPDR and PDR). It was also found that the average folic acid levels of patients without DR were higher than those with DR. Therefore, it was found that folic acid was related to the incidence of DR but not related to the severity of DR. This aligns with the previous research conducted by Malaguarnera G et al. <sup>22</sup> , which found that diabetic patients with

Proliferative Diabetic Retinopathy (PDR) and Non-Proliferative Diabetic Retinopathy (NPDR) exhibited significant deficiencies in plasma folic acid and red blood cell folate compared to healthy subjects and diabetic subjects without retinopathy.<sup>22</sup> However, unlike this study, they also found a potential relationship between folic acid levels and the severity of DR. That research also found that the patients treated with metformin showed a significant decrease in folate. This has not been analyzed in this study and could possibly influence the results. Folate levels in the blood were also associated with age, sex, and severity of retinopathy in that study.<sup>22</sup> The findings of this study are also consistent with the research by Lei XW, et al.<sup>23</sup>, which demonstrated that folic acid acts as a potential therapeutic agent targeting multiple signaling cascades in diabetic retinopathy. Consequently, a protective effect against early-stage retinal thinning in diabetic retinopathy was observed.<sup>23</sup>

Meanwhile, there was a significant positive correlation with moderate strength between homocysteine levels and retinal non-perfusion areas, implying that higher homocysteine levels are associated with increased retinal non-perfusion area. Conversely, the study found a significant negative correlation of moderate strength between homocysteine levels and vascular density, suggesting that higher homocysteine levels are associated with lower vascular density in the retina. Homocysteine has been researched as a biomarker and risk factor for vascular disease, including vascular disease of the eye.<sup>1</sup> An increase in homocysteine is associated with increased oxidative stress. In the pathogenesis of diabetic retinopathy, oxidative stress and mitochondrial dysfunction initiate the development of the characteristic histopathology of DR.<sup>1,24</sup> High homocysteine can damage mitochondria, accelerate capillary cell apoptosis, and the progression of diabetic retinopathy. Inhibiting hyperhomocysteinemia in diabetic patients may help prevent the progression of DR.<sup>24</sup> Several studies have found that homocysteine is related to the severity of DR.<sup>25,26</sup> A study by Tawfik A et al.<sup>27</sup> showed an increase in homocysteine levels in the serum, vitreous, and

retinas of diabetic patients and animal models of diabetes. Additionally, homocysteine was found to induce changes in the retinas of rats, which worsened under diabetic conditions. According to that study, homocysteine can be used as a biomarker in DR screening. Therapeutic targeting with homocysteine clearance could also be a future therapy for DR.<sup>27</sup> A meta-analysis by Lei X et al.<sup>17</sup> regarding the relationship between homocysteine levels and the risk of diabetic retinopathy also showed that increased homocysteine levels were associated with an increased risk of diabetic retinopathy, especially in patients with type 2 diabetes.<sup>17</sup> This is consistent with this study that found a significant difference in serum homocysteine levels across all groups ( $p = 0.008$ ). Therefore, it is necessary to conduct serum homocysteine examinations in patients with diabetes mellitus to screen microvascular complications, particularly Diabetic Retinopathy.

Optical Coherence Tomography Angiography (OCTA) effectively visualizes retinal microvascular features, aiding in accurate Diabetic Retinopathy (DR) classification.<sup>28</sup> This study found significant differences in vascular density and retinal non-perfusion area across all groups. Previous research corroborated these findings, showing that DR patients have lower perfusion density, vessel length density, and fractal dimension compared to healthy eyes.<sup>29</sup> Further studies also noted marked differences in the avascular foveal area and vascular density between DR patients and healthy individuals, along with significant variations in retinal thickness and vessel density in different DR stages.<sup>30</sup>

This study has several limitations including the nature of the cross-sectional study, the low number of research samples, and other variables that could affect homocysteine and folic acid levels have not been specifically identified. Further research is needed on the role of folic acid and homocysteine in the severity of DR with other parameters and the influence of other substances that may affect the severity of DR. It is expected that this study can contribute to further research on examinations and therapies for DR.

## Conclusion

This study discovered significant correlations between folic acid and homocysteine levels with retinal conditions. Folic acid levels correlated with retinal non-perfusion area and vascular density in the retina. A notable difference was also found between patients without DR and those with DR, with higher average folic acid levels in patients without DR, suggesting a potential protective role against DR. Additionally, the study noted a correlation between homocysteine levels and retinal non perfusion area. There is also a correlation between homocysteine levels and vascular density. Serum homocysteine showed a significant difference in the severity of DR. This highlights homocysteine as a potential biomarker for DR severity and a target for therapeutic intervention. This study's findings suggest that regular monitoring of homocysteine serum and folic acid levels is useful in predicting the risk and progression of DR. Additionally, folic acid supplementation could potentially prevent or treat DR, though this warrants further investigation and confirmation through clinical trials. This research adds to the growing evidence of the importance of folic acid and homocysteine serum in DR and underscores the value of OCTA in the early detection and classification of DR.

## Conflict of interest

The authors declare that no conflict of interest with another person or institution.

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CASE REPORT

## Enteral nutrition with medium-chain triglyceride compared to total parenteral nutrition in patient with chylothorax: an evidence based case report

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### Abstract

**Introduction:** Chylothorax is associated with longer length of stay, higher morbidity, mortality, and hospitalization cost. The main principle of chylothorax therapy is to reduce the chylous flow. The current nutritional management of patients with chylothorax are a low fat diet with long chain triglyceride (LCT) restriction, enteral nutrition with high medium chain triglyceride (MCT), and total parenteral nutrition. However, low fat diet with LCT restriction takes quite a long time (around 3 weeks) and requires close monitoring due to risk for malnutrition, essential fatty acid, and micronutrient deficiencies. The nutritional management determines the success of conservative therapy in chylothorax patients. The aim of this study was to determine whether a high MCT enteral diet is more superior than total parenteral nutrition regarding the resolution of chylothorax.

**Method:** Literature searching was conducted using advanced searching in three large databases: Pubmed, Science Direct, and ProQuest using eligibility criteria determined by the authors. Quality of evidences were assessed based on GRADE Guidelines. Level evidence was determined based on Oxford Center of Evidence-based Medicine (CEBM).

**Result:** Three systematic reviews and one cohort met the PICO and eligibility criteria that had been set. Two studies concluded that enteral nutrition was better than parenteral nutrition. One study concluded that parenteral nutrition could be considered first and one study could not conclude which kind of nutrition was better.

**Conclusion:** Administration of high MCT enteral nutrition can be the first line therapy in patients with chylothorax and still need close monitoring during the administration. One of the factors that need to be monitored is the daily production of chylothorax volume. The results shown by these studies are inconsistent and warrant further research of high-quality studies regarding the treatment of chylothorax.

**Keywords:** total parenteral nutrition, enteral nutrition, low fat diet, MCT, chylothorax

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## Case Scenario

Mr. A, 53 years old, has been admitted to the hospital with chief complaint of severe shortness of breath one day before admission. The patient was then using water seal drainage (WSD) and the initial production was 1200 mL in 24 hours-serous. Two days later, the color of the WSD became white like milk with daily production reaching 1500 mL per day. The laboratory results showed total cholesterol in the pleura was 76 mg/dL, pleural triglyceride was 713 mg/dL, total blood cholesterol was 179 mg/dL, and serum triglycerides were 161 mg/dL. Pleural fluid analysis showed positive rivalta test, count cell 3834 with PMN 1717 and MN 2117, protein ratio 0.61, LDH ratio 0.96, with the conclusion chylous effusion. The patient was diagnosed with chylothorax. The thoracic and cardiovascular surgeon then consulted to a clinical nutrition specialist regarding the diet for this patient with chylothorax. The doctor asked whether enteral nutrition with high MCT is better than total parenteral nutrition.

## Introduction

Chylothorax is a condition where there is accumulation of chyle in the pleural cavity. Chyle is the milky bodily fluid formed in the lacteal system of the intestine. The etiology of chylothorax can be classified into traumatic and non-traumatic. Non-traumatic chylothorax can be caused by congenital, neoplasms (lymphoma, leukemia, lung cancer, or esophageal cancer), infection which is a complication of tuberculous lymphadenitis, and several other rare cases such as essential fatty acid, and micronutrient

deficiencies. Long chain triglyceride restriction diet is highly unpalatable, hence lowering the adherence of the patients. Enteral formulas containing MCT can provide macronutrients and micronutrients needed. TPN contains provides nutrients through the veins, thus avoiding the absorption of LCT into the lymphatic through the intestine and in other hand still provide essential fatty acid needed. However,

as cattleman's disease, sarcoidosis, or Kaposi's sarcoma. Malignancy is the most common cause of non-traumatic chylothorax.<sup>1</sup> Traumatic chylothorax can be caused by postoperative, blunt, or sharp trauma. Postoperative chylothorax is the most common cause of chylothorax. Incidence of chylothorax ranges from 0.5 to 2%, but mortality rate is up to 50% due to nutritional deficiency, dehydration, and immunosuppression. It is also associated with a longer duration of hospitalization, higher morbidity and mortality rates, and higher hospitalization cost.<sup>2</sup>

The diagnosis of chylothorax can be obtained from the result of pleural fluid analysis, pleural triglycerides >110 mg/dL and total pleural cholesterol <200 mg/dL.<sup>1,3</sup> Management of chylothorax can be therapeutic or surgical. Surgical treatment is considered invasive meanwhile conservative treatment is effective especially for low flow-rate chylothorax (<800 mL/day).<sup>4</sup> One of the important factors in conservative therapy in patients with chylothorax is the nutritional management used.<sup>5</sup> The principal treatment of the chylothorax is to reduce the chyle outflow so that the leak resolves on its own. Consequently, the conventional management of the chylothorax is to put the patient in a fasting state. If the patient puts in fasting state for quite long time, this can lead into malnutrition. Therefore, studies are looking for the best option for nutrition in chylothorax. Current nutrition management strategies for chylothorax patients are long chain triglyceride restriction diet, high medium chain triglyceride enteral nutrition, and total parenteral nutrition. However, low fat diet with LCT restriction takes quite a long time (around 3 weeks) and requires close monitoring due to risk for malnutrition,

long term PN would weaken the intestinal function and lead to further complications.<sup>2</sup>

The most ideal nutritional strategy including the duration of nutritional administration is one of the components that determine the success of conservative therapy in patients with chylothorax. Considering the difficulty of dietary adherence, the risk of infectious malnutrition, and essential fatty acid deficiencies, the provision of nutrition

to patients with chylothorax must be given appropriately and efficiently.<sup>2</sup>

## Clinical Question

P : Patients with chylothorax  
I : High MCT enteral nutrition  
C : Total parenteral nutrition  
O : Resolution of chylothorax

Clinical question: Is a high MCT enteral diet compared to total parenteral nutrition better for resolution of chylothorax?

## Methods

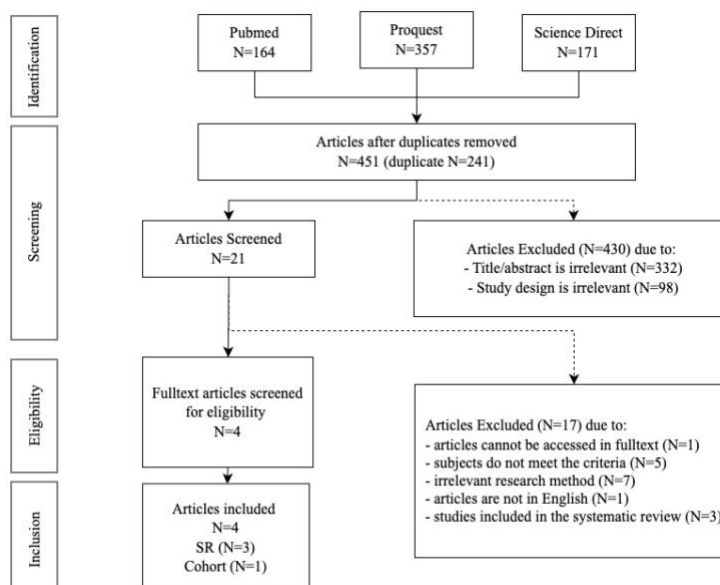
Literature searching was performed using combination of MeSH terms and Title/Abstract on three large databases: Pubmed, Science Direct, and ProQuest. Search was carried out on June 5, 2023. The keywords used were “total parenteral nutrition”, “enteral nutrition”, “MCT”, “medium chain triglyceride”, “chylothorax”, “chyle leaks”, “chylous leaks”, “chylous thorax”, “parenteral nutrition”. Critical assessment tools and levels of evidence are based on the Oxford Center for Evidence-Based Medicine.

## Eligibility criteria

Inclusion criteria including subjects between 18 to 65 years of age with chylothorax, study design was cohort, systematic review/meta-analysis, and one of the outcomes is the resolution of the chylothorax, published between year 2019 to 2023, and was written in English. Exclusion criteria including animal study and article not available in full text.

## Results

The author found 164 articles in Pubmed, 357 articles in Proquest and 171 articles in Science Direct. Duplicate removal was performed using Zotero. The articles were assessed for eligibility criteria based on PICO, resulting in the selection of four articles as shown in **Figure 1**. There are three systematic review and one cohort that met the eligibility criteria. The study characteristics of these articles were listed in **Table 2**. The level of evidence for these articles is presented in **Table 3**, and all the articles were found to be relevant for answering the clinical question (**Table 4**)



**Figure 1.** Prisma's flowchart



**Table 1.** Resources and search strategy

Database	Terminology	Hits	Eligible
<b>Pubmed</b>	("total parenteral nutrition" [MeSH Terms] OR "parenteral nutrition" [MeSH Terms] OR "enteral nutrition" [MeSH Terms] OR "MCT" [MeSH Terms] OR "medium chain triglyceride" [MeSH Terms]) AND ("chylothorax" [MeSH Terms] OR chyle leaks" [MeSH Terms] OR "chylothorax" [MeSH Terms])	164	1
<b>Proquest</b>	(total parenteral nutrition OR parenteral nutrition OR enteral nutrition OR MCT OR medium chain triglyceride) AND (chyle leaks OR chylothorax OR chylous leaks)	357	2
<b>Science Direct</b>	(total parenteral nutrition OR parenteral nutrition OR enteral nutrition OR MCT OR medium chain triglyceride) AND (chylothorax OR chyle leaks OR chylous thorax)	171	1

**Table 2.** Study characteristic

Author	Study Design	Population Characteristic	Total Participants	Outcome	Key Results
Power R, <i>et al</i> <sup>7</sup> (2021)	Systematic review	Postoperative patients with chylothorax	726 (N=16 studies)	Technical success rate, clinical success rate, resolution time after chyle leaks, complication from procedure	<ul style="list-style-type: none"> <li>3 studies using enteral nutrition (EN)</li> <li>16 studies using parenteral nutrition (PN)</li> <li>Clinical success rate of PN 11-100%</li> <li>Clinical success rate of EN 38-83%</li> <li>Resolution time using PN has median 5-35 days</li> <li>Resolution time using EN has median 9 days.</li> </ul>
Zheng J, <i>et al</i> <sup>8</sup> (2020)	Cohort Retrospective	Postoperative patients with chylothorax, got at least three days of nutritional management	38	Nutrition cost, treatment cost, time of resolution, duration of drain installation, length of stay, duration until surgery, duration from surgery to diagnosis of chylothorax.	<ul style="list-style-type: none"> <li>Enteral nutrition + MCT was significantly less expensive than total parenteral nutrition (p=0.00)</li> <li>The cost of hospitalization in patients with enteral nutrition + MCT was significantly less expensive compared to total parenteral nutrition (p=0.001)</li> <li>Resolution time for chylothorax in patients with enteral nutrition + MCT compared with total parenteral nutrition was not significantly different (p=0.260)</li> <li>The duration until surgery in patients with</li> </ul>

Author	Study Design	Population Characteristic	Total Participants	Outcome	Key Results
					enteral nutrition + MCT compared with total parenteral nutrition was not significantly different (p=0.654)
Smith R, et al. <sup>9</sup> (2022)	Systematic Review	Postoperative patients with chylothorax	30 (N=10 studies)	Resolution of chylothorax	<ul style="list-style-type: none"><li>• Duration from surgery to diagnosis of chylothorax in patients with enteral nutrition + MCT compared to total parenteral nutrition was significantly different (p=0.01)</li><li>• 7 cases resolved after receiving non-nutritional or surgical treatment</li><li>• 7 cases resolved after receiving TPN</li><li>• 15 cases resolved after given MCT-based enteral diet</li><li>• 1 case resolved after given low-fat diet</li><li>• The average duration of TPN use was 3 weeks</li><li>• The average duration of MCT enteral diet was 15 days.</li></ul>
Robinson AV, et al. <sup>10</sup> (2022)	Systematic review	Postoperative patients with chylothorax and undergo conservative therapy	838 (N= 21 studies)	Resolution of chylothorax	<ul style="list-style-type: none"><li>• Success rate using MCT as a nutritional intervention is 57.9%</li><li>• Success rate using TPN as the main nutritional intervention 51.5%.</li></ul>

EN: Enteral Nutrition; MCT: Medium Chain Triglyceride; PN: Parenteral Nutrition, TPN: Total Parenteral Nutrition

**Table 3.** Validity criteria

	P I C O	Review Strategy	Study Design	Study Quality Assessment	High Quality	Results in Tables/ Forest Plots	Similarity of Study Results	Quality of evidence*	Level of evidence**
Power R, et al. <sup>7</sup>	+	+	+	+	-	+	+	Low	1
Zheng J, et al. <sup>8</sup>	+	+	+	+	+	+	+	Low to Moderate	3
Smith R, et al. <sup>9</sup>	-	+	+	+	-	+	+	Low	1
Robinson AV, et al. <sup>10</sup>	+	+	+	+	+	+	+	Low to moderate	1

\* Quality of evidence according to GRADE guidelines, <https://www.ncbi.nlm.nih.gov/pubmed/21208779>

\*\*Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), <http://www.cebm.net>.

+ clearly mentioned in the article; - not done; ? Not stated clearly

**Table 4.** Relevance criteria

Authors	Similarity Population	Similarity determinant/intervention/indicators	Similarity Outcome
Power R, <i>et al</i> <sup>7</sup>	+	+	+
Zheng J, <i>et al</i> <sup>8</sup>	+	+	+
Smith R, <i>et al</i> . <sup>9</sup>	+	+	+
Robinson AV, <i>et al</i> . <sup>10</sup>	+	+	+

+ clearly mentioned in the article; - not done; ? not stated clearly

**Discussion**

There are four articles reviewed in this paper. Two of four articles reviewed stated enteral nutrition was better than parenteral nutrition. One study stated that parenteral nutrition can be considered first, and one study cannot conclude which nutrition was better.

Nutritional management plays an important role in chyle leak cases to maintain adequate caloric intake and minimize the volume of chyle passing through the thoracic duct, giving time for the lymphatic system to heal and close. There are several approaches to providing nutritional therapy in patients with chylothorax. Modifying a low-fat oral diet is one of the preferred options using a high protein and low fat (<10 grams of fat per day) diet. By reducing the amount of fat absorbed, it is hoped that there will be a decrease in chylous flow and in the accumulation of chylous in the pleural space. Patients are also advised to avoid consuming long-chain triglycerides (LCT).<sup>11</sup> However, low fat diet with LCT restriction takes quite a long time (around 3 weeks) and requires close monitoring due to risk for malnutrition, essential fatty acid, and micronutrient deficiencies.<sup>6</sup> Enteral nutrition can also be given as supplement for patients with chylothorax. High-MCT enteral nutrition will be transported directly through the liver to the portal vein without crossing the thoracic duct. Another option is total parenteral nutrition containing carbohydrate, protein, and fat. In total parenteral nutrition, no fat restriction is needed because the fat will be given intravenously.<sup>11</sup>

Systematic review from Power R *et al*.<sup>7</sup> compared conservative therapy and surgery in patients with chyle leaks post esophagectomy. This study is the largest study that evaluates the therapy in cases of post-operative chyle leaks. The

outcomes assessed in the study were success rate, clinical success, time required to resolve the chylous leak, and complications from the procedure. Sixteen out of 25 studies (726 patients) in the systematic review underwent conservative therapy.

Conservative therapy is by giving total parenteral nutrition and enteral diet modification. Twelve out of 16 studies undergoing conservative management provided total parenteral nutrition with success rates ranging from 11-100%. The rest of the studies used an enteral feeding approach with high MCT, with the percentage of success rate ranging from 38-83%. However, study from Power R *et al*.<sup>7</sup> did not conclude which type of nutrition was better.

A systematic review from Smith<sup>9</sup> assessed proper nutritional management in chyle leaks cases. The options were giving a low triglyceride diet with MCT supplementation, enteral feeding with MCT, or total parenteral nutrition. This study assessed 31 cases related to chyle leakage. Seven cases were resolved after the administration of total parenteral nutrition, 15 of them were resolved after the administration of enteral nutrition, one resolved after the administration of a low-fat diet, and the rest were by non-nutritional intervention.

Study from Smith<sup>9</sup> explained the discrepancy between the duration of the therapy from two types of nutrition administration. The average duration of total parenteral nutrition was three weeks, while using the enteral MCT diet was 15 days. The heterogeneity in this study was high; therefore, the meta-analysis cannot be carried out. Smith<sup>9</sup> concluded that nutritional management is the main therapy for chyle leaks. Reducing chylous production can be decreased by restricting fat intake and supplementation with MCTs. Oral intake can still be given in the

rehabilitation process. Based on this study, the administration of enteral nutrition with high MCT is still the main and first choice in patients with chylothorax. However, this study acknowledges the need for more high-quality evidence regarding chylothorax.

A retrospective study from Zheng J et al.,<sup>8</sup> analyzed patients with chylothorax in 2014- 2018 at the West China Hospital of Sichuan University. The strength of this study is that the researchers included specific inclusion criteria for the nutritional intervention given. All patients must receive nutritional management for at least three days and if the patient receives total parenteral nutrition, it has to be given with total calories above 60% of daily needs, and oral nutrition must meet at least 400 kcal/day. Nutrition received by patients can be divided into four classifications: a group of those who received MCT enteral nutrition (MCT being the only source of lipids), patients on the MCT diet (low-fat diet cooked with oil sourced from MCT), MCT enteral nutrition and the MCT diet (enteral nutrition high MCT being the supplementation of the additional diet obtained), and total parenteral nutrition. This study compared the group receiving enteral nutrition with MCT (group E) and total parenteral nutrition (group T). It was found that there were significant differences in the aspect of nutritional costs and overall medical costs between the two groups. The group that received parenteral nutrition had a higher total cost than the other groups. Interestingly, there was no significant difference between the two groups regarding resolution time and length of hospital stay. Zheng et al.,<sup>8</sup> recommend giving enteral nutrition with high MCT as the first line therapy before giving total parenteral nutrition considering the risk of giving total parenteral nutrition, such as venous infection and liver disorder, so enteral nutrition is considered safer and more natural.

A systematic review from Robinson<sup>10</sup> assessed 21 studies consisting of 814 chyle leak cases with different therapeutic approaches. One study by Weijs et al.,<sup>12</sup> showed a success rate of up to 65.6% in the population given a low-fat diet for seven days in patients with chyle leaks <500 mL/day. Meanwhile, the total parenteral nutrition

approach was used in at least 378 cases (47.5% of the population).<sup>12</sup> Based on the review of these studies, treating chyle leaks is highly variable, and it is difficult to determine the most optimal therapeutic strategy. Three clinical trials in this study stated fat restriction is the last option, preferred in cases with a low volume of drain (<500 mL/day). Based on a study from Robinson<sup>10</sup>, if the initial production is higher than 500 mL per day, total parenteral nutrition is preferred.

There is a limited available study in this systematic review. Of 21 studies obtained, 20 were with level II evidence, and only one was a clinical trial. However, the clinical trial needed to state the method of randomization and blinding used clearly. Therefore, the validity was doubtful. It should be considered that the decision to perform surgery or end the conservative therapy in most studies still uses clinical judgment. There are no benchmarks that determine the failure of conservative therapy.<sup>10</sup>

A systematic review from Steven and Carey<sup>13</sup> highlighted the role of nutrition in patients with chylothorax. This study concluded that the MCT diet had a success rate of 77.3% which was higher than total parenteral nutrition, which was 68.5%. The combined administration of the MCT diet and total parenteral nutrition had a slightly higher success rate, namely 77.6%. However, it cannot be concluded that total parenteral nutrition is more ineffective in patients with chylothorax because the population with the administration of total parenteral nutrition has a higher amount of drain production.

In determining the type of nutrition that should be given, the volume of chylothorax needs to be considered. The Esophagectomy Complications Consensus Group (ECCG) classification also classifies chyle leaks into three types and two severities. Type I only requires modification of enteral diet, type II requires total parenteral nutrition, and type III requires intervention or surgical therapy. Based on the severity level, level A is those with chyle production less than one liter per day, and level B is those with chyle production of more than one liter per day.<sup>14</sup> However, until now, there is no definite consensus on which

states the main therapy for each type and severity of chyle leaks.

One of the studies in the systematic review of Robinson<sup>10</sup>, Weijs, et al.,<sup>12</sup> explained that an enteral diet can be given if drain production is less than 500 mL per 24 hours, but if the production is 500-1000 mL per 24 hours, it is recommended to give total parenteral nutrition for at least seven days. Weijs, et al.,<sup>12</sup> shows that the production of chylothorax fluid also influences the decision to choose nutritional therapy.<sup>8</sup>

Based on the protocol from Smith<sup>7</sup>, the chylous volume, whether it is less than or more than 1000 mL, will still be given the enteral nutrition with high MCT as the first-line treatment. Nevertheless, if the response afterward needs to be revised, the next step approach will be different. In a population with chylous production of less than 1000 mL per day and not reduced after administration of the MCT diet, it is recommended to combine with octreotide first, whereas in patients with daily production of more than 1000 mL per day and not responding to MCT diet, it is suggested to start parenteral nutrition.

Study characteristic from Zheng<sup>8</sup> shows that the volume of chylothorax in the study population ranges from 171.86 mL to 639.24 mL. This study cannot be classified as high-output chylothorax. Therefore, this might be why giving enteral or total parenteral nutrition in this study did not have a significant difference.

Assessment, analysis, and conclusion from these studies are difficult due to the lack of studies with high levels of evidence. Chylothorax is a rare event with high potential to cause complication, morbidity, and mortality.<sup>13</sup> The difficulties in conducting studies related to chylothorax are: (1) low incidence (0.3-2.3%), (2) the definition of chyle leaks and high output chylothorax are different in each center, (3) it is difficult to determine the timing of chylothorax occurred, and (4) rapid change of condition that requires modification of dynamic management.<sup>4,7</sup> These are the factors why studies related to chylothorax have low quality. All the SRs found cannot make a meta-analysis due to the heterogeneous study population.

Making conclusions from these studies has become more difficult due to various choices of therapy that have been given as a part of conservative therapy in patients with chylothorax. Therapies that have been given are octreotide, ethylenephine, and pleurodesis.<sup>8,15</sup> In addition, there are many variations of nutritional therapy, making it more difficult to make a protocol.<sup>2</sup>

Palatability and patient nutritional compliance are considerations that need to be made when carrying out low-fat or high MCT enteral diet. Studies shown that feed tolerance and palatability of low LCT diet is one of the main barrier to manage chylothorax.<sup>2</sup> Enteral formula containing MCT are easier to use, but patients may not accept the taste. It is usually used for tube-fed patients. However, other kinds of food can still be given, such as clear fluid, water, fruit juice, or drinks without milk.<sup>11</sup>

Since chylothorax is a rare case, we can use the Delphi approach to determine appropriate nutritional management in patients undergoing conservative therapy.<sup>8</sup> In this case, the patient was a 53-years-old male whose production of chylothorax was more than 1000 mL per day. The characteristics and diagnosis of the patient were similar to the population in the study. Enteral nutrition with high MCT can be given first, and if the volume production is not reduced, then total parenteral nutrition can be considered.

## Conclusion

Low fat diet with LCT restriction takes quite a long time and has low adherence. Use of total parenteral nutrition or high MCT enteral nutrition in other hand are preferred in patients with chylothorax. Considering the risk of giving long-term TPN, high MCT enteral nutrition can be the first-line therapy in chylothorax patients. Close monitoring of chylothorax volume production is still needed.

Albeit the results shown from these studies are still inconsistent. There is still a lack of high-quality studies regarding the treatment of the chylothorax. The heterogeneity of the therapeutic regimens used and the variability of the treatment modalities make it more difficult to draw



conclusions regarding nutritional therapy for chylothorax. Since chylothorax is a rare case, future study can focus on using the Delphi approach to determine appropriate nutritional management in patients undergoing conservative therapy.

## Conflict of interest

Authors declared no conflict of interest regarding this article.

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CASE REPORT

## The impact of omega-3 on recurrent seizures in epileptic patients: A case study with evidence-based approaches

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### Abstract

**Background:** Epileptogenesis is also associated with increased production of excessive pro-inflammatory cytokines which shows connection between pro-inflammatory cytokines as triggering factor with omega-3 which has anti-inflammatory effect. Omega-3, known for its neuroprotective and anticonvulsant properties, exhibits promising effects on epileptic seizure attacks.

**Objective:** This study aimed to evaluate the effect of omega-3 supplementation on the incidence of seizures in epilepsy patients.

**Methods:** This study used a literature search using advanced queries in the databases PubMed, Scopus, ProQuest, and Cochrane Library, and combined MeSH terms with Title/Abstract. The collected literature is discarded if there are duplicates, then literature is filtered that meets the eligibility criteria. We used the Oxford Center for Evidence-Based Medicine as a means of critical appraisal and determining the level of evidence of the selected literature.

**Results:** Four chosen literatures were critically assessed. Two articles indicating no significant difference between omega-3 and placebo and two articles showed had a significantly higher number of seizure-free days than placebo. The first article, involving 78 adults, reported a 50% reduction in seizure risk with a frequency RR of 0.57, 95% CI 0.19 to 1.75 (IS = 0%) indicating no significant difference between omega-3 and placebo groups after 12 weeks of treatment. The second study, comprising mostly non-significant findings, demonstrated no significant correlation between omega-3 and epilepsy attacks in epilepsy patients. The third literature revealed seizure occurrences per month in the EPA group (9.7±1.2), DHA group (11.7±1.5), and placebo group (16.6±1.5). Incidence rate ratio (IRR) adjusted for seizure type in EPA and DHA groups compared to the placebo group were 0.61 (CI = 0.42–0.88, p = 0.008, a 42% reduction) and 0.67 (CI = 0.46–1.0, p = 0.04, a 39% reduction), respectively. Both treatment groups had a significantly higher number of seizure-free days compared to the placebo group (p < 0.05). The fourth study reported intervention group frequency (4.72 ± 1.6, p= 0.014) and placebo frequency (11.64 ± 1.63, p=0.014) with intervention group seizure duration (6.64 ± 1.39, p=0.009) compared to placebo group (14.36 ± 2.18, p=0.009).

**Conclusion:** Omega-3 supplementation may be considered for management in patients with recurrent epileptic seizures, although its effect on reducing seizure frequency remains inconsistent.

**Keywords:** epilepsy, recurrent epilepsy, case study, omega-3 fatty acid

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## Case report

A 20-year-old male, referred by a neurologist to a clinical nutrition specialist, has been diagnosed with symptomatic generalized tonic-clonic epilepsy. He has been struggling with recurrent seizures due to epilepsy since childhood. Vital signs and overall examinations are within normal limits. His present body mass index is 20.2 kg/m<sup>2</sup>. Laboratory tests are within normal limits, and an EEG examination reveals abnormal epileptiform activity in the left temporal region, accompanied by a focal slowing in both temporal lobes, predominantly on the left. The patient is regularly taking antiepileptic medication, Levetiracetam 2x500 mg, and Paracetamol 1000 mg for headache pain as prescribed by his neurologist. Subsequently, after reading online about the potential benefits of omega-3 in reducing recurrent seizures in epilepsy patients, he inquired about the advantages of omega-3 for patients with epilepsy, such as himself.

## Introduction

Epilepsy is a disorder caused by chronic brain abnormalities characterized by recurrent seizures due to paroxysmal changes in neurological function caused by excessive neuron discharge and hyper synchronization in the brain without identifiable precipitating factors.<sup>1,2</sup> According to the World Health Organization (WHO), the global prevalence of epilepsy is approximately 50 million people. In affluent countries, a reckoned 49 per 100,000 individuals are diagnosed with epilepsy per year, at the same time in low- and middle-income countries, it reaches 139 per 100,000 population.<sup>3</sup> In Indonesia, the prevalence of epilepsy is around 8.2 per 1,000 population, with around 50 new cases per 100,000 population yearly.<sup>4</sup> Patients with recurrent epileptic seizures may experience disruptions in daily activities, impacting the overall quality of life for individuals with epilepsy.<sup>5,6</sup>

Epilepsy occurs when neurons in the epileptogenic focus have a lessened stimulus threshold, making the irritated neurons easily triggered by physiological changes that as fatigue,

lack of sleep, stress, fever, constipation, structural disorders, infections, or metabolic disturbances. In adults without a genetic predisposition to epilepsy, usual etiologies for seizures include encephalitis/meningitis, traumatic brain injury, and brain tumors.<sup>7</sup> The pathophysiology of epilepsy arises from an imbalance between excitatory and inhibitory stimuli in the epileptic focus. When excitatory stimuli exceed inhibitory stimuli, abnormal high depolarization occurs, causing a series of action potentials. Known processes contributing to neuronal depolarization include calcium and sodium influx, potassium efflux, excitation through amino acids (such as glutamate), and inhibition through neurotransmitters (GABA). Epileptogenesis is also associated with increased production of excessive pro-inflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$  and interleukin-6 (IL-6).<sup>8,9</sup> Epilepsy treatments, including phenytoin, carbamazepine, and valproic acid, along with non-pharmacological interventions such as lifestyle modifications, and an area still under investigation is the administration of anti-inflammatory supplements like omega-3 to control seizures.<sup>10</sup>

Omega-3 fatty acids are polyunsaturated fatty acids with multiple double bonds. The three most crucial omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which cannot be endogenously synthesized and must be obtained from dietary sources. Omega-3 fatty acids play a functional role in physiological processes within the brain.<sup>11</sup> In epilepsy, omega-3 can reduce inflammation by inhibiting the formation of pro-inflammatory eicosanoids (EPA), suppressing NF- $\kappa$ B, and decreasing the release of pro-inflammatory cytokines such as TNF- $\alpha$ . EPA can reduce the expression of TNF- $\alpha$ , IL-6, and prostaglandin E, and suppress TNF- $\alpha$  and IL-6 in hepatocytes.<sup>12</sup>

Research demonstrating the effects of omega-3 supplementation in reducing the frequency and duration of seizures in patients with refractory epilepsy includes a study by Omrani et al.<sup>13</sup> In this study, 50 patients with refractory epilepsy were divided into two groups,

placebo, and control, with the control group receiving omega-3 fatty acid capsules containing 120 mg DHA and 180 mg EPA twice daily. Patients receiving omega-3 did not experience seizures significantly during the study period, and the levels of TNF- $\alpha$  and IL-6 decreased by 38% and 41%, respectively. This contrasts with a systematic review study by Pourmasoumi et al.,<sup>14</sup> which involved several studies that did not show a notable relationship between omega-3 and epilepsy attacks in epilepsy patients.

Based on previous research, it is not yet conclusive whether omega-3 can reduce seizure frequency in epilepsy patients. This evidence-based case report seeks to assess the impact of omega-3 supplementation on seizure attacks in epilepsy patients.

### Clinical questions

"Can omega-3 reduce seizure episodes in adult and children patient with epilepsy?"

Participants (P): adult and children patient diagnosed with epilepsy

Intervention (I): omega 3 supplementation

Control (C): placebo

Outcome (O): seizure episodes

### Methods

#### *Searching strategy*

A literature search was managed using an advanced search with a combination of MeSH Terms and Titles/Abstracts in four databases: PubMed, Cochrane Library, Scopus, and Proquest. Keywords included "epilepsy," "epilepsy syndrome," "omega-3," "omega-3 eicosapentaenoic," "omega-3 fatty acid," "n-3 unsaturated fatty acid," "placebo," and "epileptic seizure." The Oxford Centre for Evidence-Based Medicine guidelines were utilized for critical literature assessment and determining the level of evidence.

#### *Eligibility criteria*

Inclusion criteria: 1) adult and children diagnosed with epilepsy; 2) patients receiving omega-3 supplementation; 3) research outcome focusing on seizure episodes; 4) study design being a controlled clinical trial or a systematic review/meta-analysis of randomized controlled trials; 5) articles published in English.

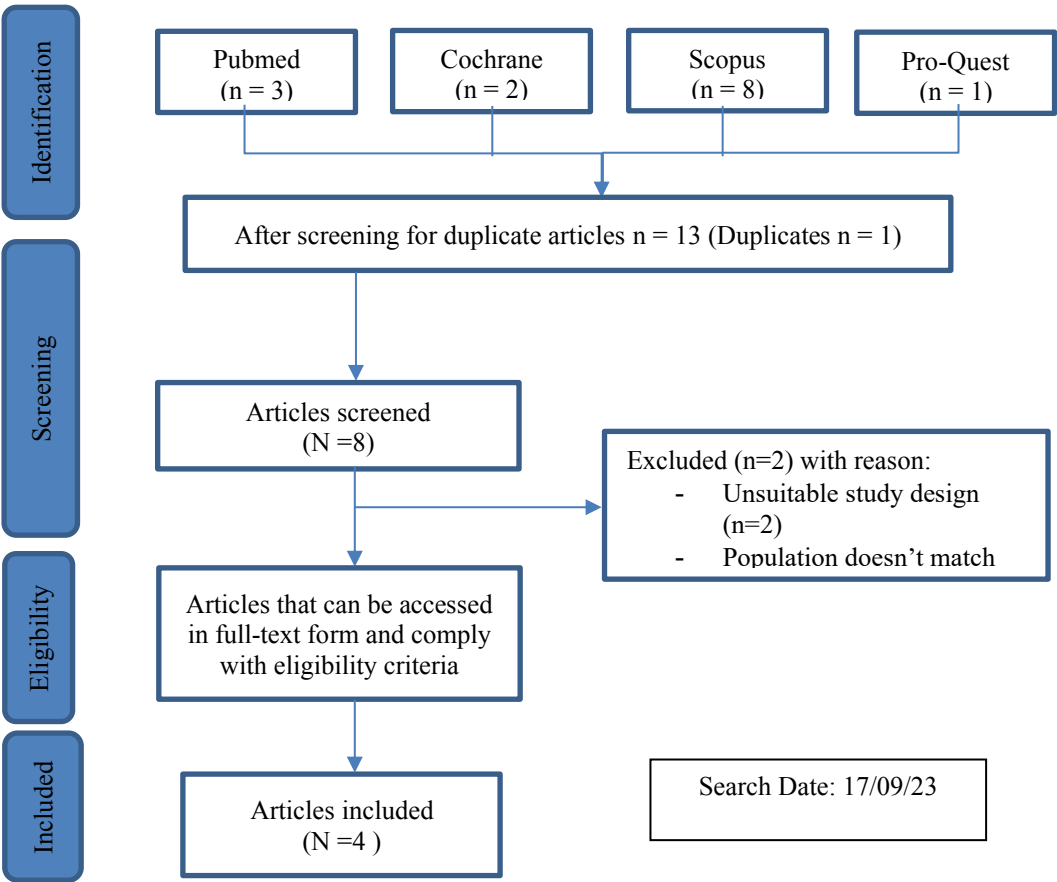
Exclusion criteria: 1) studies not conducted on humans; 2) articles not available in full text.

### Results

The selected articles met eligibility criteria through systematic reviews, meta-analyses, and controlled clinical trials. Inclusion criteria were as follows: 1) epilepsy patients, 2) utilization of omega-3 supplementation, 3) research outcomes indicating a reduction in seizure frequency, 4) articles adopting systematic review-meta-analysis or randomized controlled trials (RCT) study designs, 5) articles written in English, and 6) research involving human subjects. Exclusion criteria included articles lacking full text. The literature search was independently conducted across four databases: PubMed, Cochrane Library, Embase, and ProQuest. The literature search process is depicted in Figure 1. Keywords employed were "epilepsy," "epilepsy syndrome," "omega-3," "omega-3 eicosapentaenoic," "placebo," and "epileptic seizure." Additionally, a review using Mendeley was performed subsequently to exclude duplicate articles. The research will be critically assessed using the Oxford Centre of Evidence-based Medicine (CEBM) critical appraisal tool for systematic reviews and meta-analyses by two authors. This assessment evaluates the aspects of study validity, significance, and applicability. This study obtained literature from PubMed (3 articles), Cochrane Library (2 articles), ProQuest (1 article), and Scopus (8 articles) as shown in **Table 1**. Duplicate screening was conducted using Mendeley. Subsequent screening was based on methods, title-abstract, PICO criteria, and full-text availability. The screening results are illustrated in **Figure 1**.

**Table 1.** Literature searching strategy

Database	Search Strategy	Hits
Pubmed	(((((epilepsy[Title/Abstract]) OR (epilepsy[MeSH Terms])) OR (epilepsy syndrome[Title/Abstract])) OR (epilepsy syndrome[MeSH Terms])) AND (((omega 3[Title/Abstract]) OR (omega 3[MeSH Terms])) OR (omega 3 eicosapentaenoic acid[Title/Abstract])) OR (omega 3 eicosapentaenoic acid[Title/Abstract]))	3
Cochrane	ID Search Hits #1 (epilepsy):ti,ab,kw (Word variations have been searched) #2 (epilepsy syndrome):ti,ab,kw (Word variations have been searched) #3 MeSH descriptor: [Epilepsy] explode all trees #4 #1 OR #2 OR #3 #5 ("omega 3 fatty acids"):ti,ab,kw (Word variations have been searched) #6 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees #7 #5 OR #6 #8 ("placebo"):ti,ab,kw (Word variations have been searched) #9 MeSH descriptor: [Placebos] explode all trees #10 #8 OR #9 #11 (epileptic seizure):ti,ab,kw (Word variations have been searched) #12 MeSH descriptor: [Seizures] explode all trees #13 #11 OR #12 #14 #4 AND #7 AND #10 AND #13	2
Scopus	TITLE-ABS-KEY ( epilepsy ) OR TITLE-ABS-KEY ( epilepsy AND syndrome ) AND TITLE-ABS-KEY ( omega 3 ) AND TITLE-ABS-KEY ( placebo ) AND TITLE-ABS-KEY ( epileptic AND seizure )	8
ProQuest	title(epileptic seizure) AND title(omega 3)	1



**Figure 1.** Prisma's flow chart

**Table 2.** Characteristics of the study

Researcher	Design	Population/Intervention	Research result
Vancelos, et al., (2016) <sup>15</sup>	Systematic review/Meta-Analysis of Randomized Controlled Trials consisting of 3 RCT. <sup>15</sup>	RCT: Adult and pediatric epilepsy patients taking Omega-3 supplementation.	The average frequency of seizures, other side effects, and secondary effects, namely Quality of Life in Epilepsy (QOLIE-31).
Pourmasoumi, et al., (2018) <sup>14</sup>	Systematic review/Meta-Analysis of Randomized Controlled Trials consisting of 9 RCTs.	RCT: Nine articles with 230 patients. The intervention group received Omega-3 fatty acid supplements (1100 mg/day) with doses of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and alpha-linolenic acid (5 g/day). And in other studies, it contains 565 mg EPA/day. The average duration of the study was $22 \pm 15.27$ weeks.	Epileptic attacks.
Ibrahim, et al., (2018) <sup>16</sup>	Randomized Double-Blinded Controlled Trial	Ninety-nine (n = 99) subjects with drug-resistant epilepsy (DRE), aged 5–16 years (n = 85) and 17–45 years (n = 14). After randomization, subjects were given two, four, or six DHA capsules per day (417.8 mg DHA and 50.8 mg EPA/capsule, n = 33), EPA (385.6 mg EPA and 81.2 mg DHA/capsule, n = 33), or placebo (high oleic acid sunflower oil, n = 33) for one year.	Seizure incidence, seizure incidence rate ratio (IRR) adjusted for seizure type, difference in IRR between EPA and DHA groups, and number of seizure-free days.
Omrani, et al., (2019) <sup>13</sup>	Randomized Triple-Blinded Controlled Trial	50 patients with recurrent epileptic seizures. The intervention group received omega-3 FA supplementation, 180 mg eicosapentaenoic acid (EPA), and 120 mg docosahexaenoic acid (DHA), and the control group received placebo capsules given twice a day to each group for 16 weeks.	Frequency and duration of seizures in the intervention group compared to the placebo group.

**Table 3.** Validity criteria for the studies by Vancelos et al. and Pourmasoumi et al.

	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogeneity	Result	Applicability	Level of evidence
Vasconcelos, et al., (2016) <sup>15</sup>	Systematic Review / Meta-Analysis of Randomized Controlled Trials	+	+	+	+	+	+	A	-	Level 1A
Pourmasoumi, et al., (2018) <sup>14</sup>	Systematic Review / Meta-Analysis of Randomized Controlled Trials	+	+	+	+	+	+	B	-	Level 1A

A = In a study involving 78 adults, the risk of seizures was reduced by 50%. frequency was RR 0.57, 95% CI 0.19 to 1.75 (IS = 0%) indicating no significant difference between omega-3 and placebo groups, after 12 weeks of treatment. The estimated 50% reduction in seizure frequency after 12 weeks in a study involving single children was RR 33.00 (95% CI 4.77 to 228.15) indicating a significant difference favoring the PUFA group. B= The majority of included studies did not show a significant association between omega-3 and epileptic seizures in epilepsy patients.

**Table 4.** Validity criteria for the studies by Ibrahim et al. and Omrani et al.

Article	Study Design	Randomization	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability	Level of evidence
Ibrahim, dkk., (2018) <sup>16</sup>	<i>Randomized Controlled Trials</i>	+	+	+	+	Double-blind	C	+	Level 1B
Omrani, dkk., (2019) <sup>13</sup>	<i>Randomized Controlled Trials</i>	+	+	+	+	Triple-blind	D	+	Level 1B

C = Seizures occurred in 59 subjects (n = 59) (59.6%). The mean number of seizures per month was  $9.7 \pm 1.2$  in the EPA group,  $11.7 \pm 1.5$  in the DHA group, and  $16.6 \pm 1.5$  in the placebo group. The seizure incidence rate ratio (IRR) adjusted for seizure type in the EPA and DHA groups compared with the placebo group was 0.61 (CI = 0.42–0.88,  $p = 0.008$ , there was a 42% reduction) and 0.67 (CI = 0.46–1.0,  $p = 0.04$ , 39% reduction). There was no difference in IRR between the EPA and DHA groups ( $p = 0.56$ ). Both treatment groups had a significantly higher number of seizure-free days compared to the placebo group ( $p < 0.05$ ). D= Frequency of the intervention group ( $4.72 \pm 1.6$ ,  $p = 0.014$ ) and placebo with frequency ( $11.64 \pm 1.63$ ,  $p = 0.014$ ) and duration of seizures in the intervention group ( $6.64 \pm 1.39$ ,  $p = 0.009$ ) compared to the placebo group ( $14.36 \pm 2.18$ ,  $p = 0.009$ ).

## Discussion

The literature search yielded four studies that met the criteria. Vasconcelos et al. directed a systematic review and meta-analysis, including three selected studies: Research by Bromfield's<sup>15</sup> in 2008 research on 27 American adults divided into intervention (2.2 g/day omega-3, EPA: DHA

ratio 3:2) and placebo groups, research by Yuen's<sup>15</sup> in 2005 study on 58 individuals in the UK divided into intervention (1.7 g/day omega-3, 1g EPA and 0.7g DHA) and placebo groups, and Reda's (2015) research on 70 Egyptian children divided into intervention (3 ml/day fish oil 1200 mg, 0.24 g DHA and 0.36 g EPA) and placebo groups. All participants received interventions for



12 weeks. The study aimed to assess the benefits of Omega-3 supplementation in controlling seizures and improving the quality of life. Exclusion criteria included non-RCT studies, studies reporting only biochemical results without clinical outcomes, and incomplete data. Bias risk was assessed based on the Cochrane Handbook for Systematic Reviews of Interventions by Higgins<sup>15</sup> in 2011 for RCT studies.

Three RCTs investigating the effects of Omega-3 supplementation on epilepsy included a total of 155 subjects (85 adults and 70 children); 78 (43 adults and 35 children) were randomized to receive omega-3, and 77 (42 adults and 35 children) to receive placebo. Only one study, consisting solely of children, reported seizure freedom with omega-3 supplementation. The estimated risk for this outcome was noteworthy higher for children receiving omega-3 contrasted to the control group (risk ratio (RR) 20.00, 95% confidence interval (CI) 2.84 to 140.99, 1 study, 70 children). Likely, omega-3 supplementation was linked with a significant difference in the proportion of children with at least a 50% reduction in seizure frequency (RR 33.00, 95% CI 4.77 to 228.15, 1 study with high risk of bias, 70 children). However, this effect was not examined when data from two studies, including adult participants, were combined (RR 0.57, 95% CI 0.19 to 1.75, 12 0%, 2 studies, 78 participants, low-quality evidence). No significant differences were found between omega-3 and the control group regarding gastrointestinal effects (RR 0.78, 95% CI 0.32 to 1.89, 2 studies, 85 participants, low-quality evidence). Omega-3 supplementation did not result in considerable differences in average seizure frequency, quality of life, or side effects. This suggests that omega-3 may significantly reduce seizure freedom in children with epilepsy. However, there is insufficient evidence to support the use of omega-3 supplementation in adults with refractory epilepsy. This study need further trials with larger sample sizes to judge the benefits of omega-3 supplementation in the treatment of epilepsy with drug-resistant.<sup>15</sup>

Pourmasoumi et al.<sup>14</sup> conducted a systematic review and meta-analysis, identifying nine

clinical trial articles published between 2002 and 2015, involving 205 epilepsy patients. DeGiorgio<sup>14</sup> in 2015 used low-dose fish oil (1080 mg/day) and high-dose fish oil (2160 mg/day) in epilepsy patients with an average age of  $33 \pm 10.33$  years over 42 weeks. About 25% of participants in the low-dose fish oil group showed a 50% reduction in frequency of seizure, while 15% of high-dose fish oil participants exhibited a similar reduction compared to the placebo. About 10% of participants became seizure-free with low-dose fish oil during the intervention. No association between fish oil and seizure severity scores was found. Schlanger<sup>14</sup> in 2002 administered omega-3 supplemented bread (5 g) containing 46% DHA, 18% EPA, and 1% ALA, plus Vitamin E (100 IU) to alleviate seizures in epilepsy patients with an average age of 19 years over 24 weeks. Nonetheless, this study estimated only five patients without a control group and had a Jadad score of 0, precluding conclusions about the positive effects of omega-3.<sup>14</sup>

From the results of Yuen's<sup>14</sup> in 2005 research, it is known that patients who consumed capsules containing 1000 mg of fish oil (171 mg EPA, 112 mg DHA, <100 IU Vitamin A, and <40 IU Vitamin D) for 12 weeks experienced fewer seizures in the first 6 weeks, although this decrease was not consistent in the second 6 weeks. Research by Bromfield<sup>14</sup> in 2008 studied epilepsy patients with an average age of 36 years in the omega-3 group and 38 years in the placebo group for 4 weeks. The study revealed that patients in the intervention group (omega-3 supplement: EPA plus DHA, 2.2 mg/day with a ratio of 3:2) did not experience a reduction in seizures. The mean frequency of seizure increased to 6% in the omega-3 group and decreased to 12% in the placebo group ( $P = 0.21$ ). In a 30-week crossover study, research by DiGiorgio<sup>14</sup> in 2008 administered eight capsules containing 1200 mg of fish oil per day (216 mg EPA and 144 mg DHA) to patients (mean age 41.5 years). This study demonstrated an increase in seizure frequency of 11% in the intervention group and 14% in the placebo group ( $P = 0.051$ ), without a significant decrease in the frequency of seizures. The severity of Seizure, calculated using the

National Hospital Seizure Severity Scale, showed a non-significant decrease in mean scores from 8.55 to 7.55 in the fish oil group and from 8 to 7.57 in the placebo group.<sup>14</sup>

Research by Yuen<sup>14</sup> in 2012 evaluated the effects of 1000 mg EPA and 20 mg mixed tocopherols over 12 weeks in epilepsy patients with an average age of 49 years. The median seizure frequency reduced from 15 to 11, but it was not statistically remarkable ( $P = 0.26$ ). The study concluded that there was no significant association between EPA supplement consumption and seizure frequency. In Puri's<sup>14</sup> research in 2007, patients got three capsules containing 1000 mg fish oil (171 mg EPA, 112 mg DHA, <100 IU Vitamin A, and <40 IU Vitamin D) twice daily for 12 weeks. The average age of patients in the intervention and placebo groups was  $50.7 \pm 13.6$  years and  $40.5 \pm 12.0$  years, respectively. The results indicated that omega-3 supplementation led to biochemical changes, likely a less in phosphodiester percentage (average  $3.75 \pm 2.81$ ), an expansion in gamma-nucleotide triphosphate percentage (average  $1.73 \pm 2.41$ ), and an improvement in broadband components (BBC) (average  $13.56 \pm 7.74$ ) to evaluate brain biochemical changes potentially related to epilepsy. The study concluded that there was no connection between biochemical changes on epileptic seizures.<sup>14</sup>

Research conducted by Dahlin<sup>14</sup> in 2007 was conducted on 25 children with an average age of  $6.3 \pm 4.2$  for 12 months. 1-2 g of liquid fish oil is given and given 4 times a day. The results of the study showed that 16 children (after 3 months), 15 children (after 6 months), and 12 children (after 12 months) experienced a reduction in seizures of >50%. In serum, an increase in EPA and linoleic acid levels, a decrease in arachidonic acid (AA), and a slight increase in DHA were found. However, no association was found between changes in serum fatty acids and seizure response.<sup>17</sup>

Research conducted by Reda<sup>14</sup> et al. in 2015 in participants, the age of the intervention group was  $6.9 \pm 2.5$  years and the age of  $6.6 \pm 2.4$  years in the control group. This study used a daily dose of 3 mL containing 1200 mg of fish oil, providing

240 mg DHA and 360 mg EPA, plus Vitamin E for the intervention group, and 3 mL of corn oil daily for the control group in the study. After 12 weeks, the results showed that the frequency and severity of seizures decreased in the intervention group. Omega-3 is known to increase the seizure threshold in epilepsy patients, thereby effectively controlling the occurrence of seizures among the nine studies, research by Yuen<sup>14</sup> in 2005, DeGiorgio<sup>14</sup> in 2015, Schlanger<sup>14</sup> in 2002, and Reda<sup>14</sup> in 2015 indicated a remarkable positive correlation between omega-3 fatty acids and epileptic seizures. Despite that, the strength and quality of these studies remain low, preventing a conclusive determination of the positive outcome of omega-3 on seizure frequency. Studies by Dahlin<sup>14</sup> in 2007, DeGiorgio<sup>14</sup> in 2008, Puri<sup>14</sup> in 2007, Bromfield<sup>14</sup> in 2008, and Yuen<sup>14</sup> in 2012 did not demonstrate significant effects. Therefore, this study need research with large sample size and a long follow-up period to clarify the impact and determine the underlying mechanisms with comprehensive data.<sup>14</sup>

According to previous research by Bazan et al.<sup>18</sup>, two distinct pathways explain the effects of omega-3 on epileptic seizures. The first mechanism involves DHA regulating glutamate transporters (GLT) such as GLT1. The dysregulation of these transporters reduces glutamate concentrations, thus preventing the onset of seizures. The second mechanism, through Neuroprotectin D1 (NPD1), a derivative of DHA, exerts protective effects on the central nervous system (CNS). NPD1 enhances anti-apoptotic proteins, reduces pro-apoptotic proteins, and mitigates the effects of astrocytes and pro-inflammatory cytokines, which may lead to seizures.<sup>18</sup> According to Kavyani et al., omega-3 has an anti-inflammatory effect in reducing pro-inflammatory cytokines such as C-reactive protein, TNF- $\alpha$ , and IL-6.<sup>19,20</sup>

From the RCT study by Ibrahim et al.<sup>16</sup>, it was found that compared to the control group, the administration of omega-3 supplementation (DHA and EPA) in patients with drug-resistant epilepsy resulted in a longer duration of seizure-free days than the placebo group ( $p < 0.05$ ). This favorable effect of omega-3 on epilepsy is

associated with anti-excitatory and neuroprotective mechanisms. Omega-3 can reduce neuronal electrical activity, and inhibit repetitive stimulatory activities in cells, thus impeding the occurrence of epileptic crises. The anti-excitatory effect of omega-3 is related to the partial inhibition of ion channels on cell membranes, reducing the influx of sodium and calcium ions into cells.<sup>21</sup> Omega-3 is a crucial structural component of nerve membranes and is involved in regulating nerve functions. It diminishes the production of reactive oxygen species, byproducts of energy metabolism that can cause oxidative damage to phospholipid membranes, contributing to inflammation and neurodegeneration, thereby preventing epileptic seizures.<sup>22</sup> Additionally, omega-3 inhibits the synthesis of cyclooxygenase-2 (COX-2), an enzyme involved in pro-inflammatory production.<sup>17</sup> Omrani et al.<sup>13</sup>'s study further proves that omega-3 supplementation has the effect of elevating the seizure threshold in the supplementation group compared to the placebo. Omega-3 reduces inflammation by inhibiting pro-inflammatory cytokines, namely IL-6 and TNF- $\alpha$ , in macrophages and hepatocytes. The expression of IL-6 and TNF- $\alpha$  cytokines in astrocytes may cause a decrease in seizure threshold and an increase in seizure frequency. TNF- $\alpha$  may induce hyperexcitability of neuronal through changes in ion channels and production of glutamate, resulting in membrane depolarization and recurrent seizures.<sup>13</sup>

The four studies conducted by Vasconcelos et al.<sup>15</sup> in 2016, Pourmasoumi et al.<sup>14</sup> in 2018, Ibrahim et al.<sup>16</sup> in 2018, and Omrani et al.<sup>13</sup> in 2019 exhibit strengths and limitations. In Vasconcelos et al.<sup>15</sup>'s study in 2016, limitations include the inclusion of only a few studies in the meta-analysis, small sample sizes, and insufficient evidence supporting the supplementation of omega-3 in individuals with refractory epilepsy. Further trials are necessary to assess the benefits of supplementation of omega-3 in the treatment of epilepsy with drug-resistant (referred to specific type of epilepsy). Research results of Pourmasoumi et al.<sup>14</sup> in 2018 stated that most studies do not show a significant

relationship between omega-3 and epileptic seizures in epilepsy patients. So the benefits of omega-3 fatty acids that can have a positive effect on epilepsy patients are still controversial. Further research is needed to clarify the impact of omega-3 and determine the mechanism. future studies should use more comprehensive data, larger sample sizes, and long-term follow-up periods.

Ibrahim et al.<sup>16</sup>'s study in 2018 faces limitations such as heterogeneity in the study population concerning the frequency and types of seizures referred to specific type of epilepsy (drug-resistant epilepsy), dependence on patient-reported seizure frequency data to assess the impact of omega-3 supplementation, prolonged study duration leading to some patients discontinuing recommended antiepileptic medications, and a lack of examination of inflammatory markers due to limited research funds. This study was conducted on Sudanese patients with a traditional diet low in n-3 fatty acids. Omrani et al.<sup>13</sup>'s study in 2019 has limitations as it does not assess plasma levels of DHA and EPA in both placebo and supplemented patients before and after treatment. The small sample size is also a constraint in this research.

In the case presented, a 20-year-old male with epilepsy shares similarities in identity and diagnosis with the subjects discussed in the research. The patient can be given omega-3 supplementation to reduce seizure frequency. EPA and DHA are considered safe up to 5 g/day according to the European Food Safety Authority, and up to 3 g/day according to the US-American Food and Drug Administration. The FDA recommends that consumption of these supplements not exceed 3 grams of combined EPA and DHA per day because it has a prolonged bleeding effect as well increased risk of atrial fibrillation.<sup>23,24</sup> It safe to advise EPA: DHA ratio 1.5:1.<sup>25,26</sup> EPA:DHA ratios showed that a balanced 1:1 diet was the most effective combination to mitigate inflammation, oxidative stress and metabolic disorders.<sup>27</sup> It is advisable to recommend the consumption of omega-3-rich foods, including salmon, mackerel, tuna, herring, and sardines.<sup>28</sup>

## Conclusion

Omega-3 supplementation can serve as adjunctive therapy for patients experiencing recurrent epileptic seizures. Based on a critical review conducted in two meta-analyses and two randomized controlled trials (RCTs), omega-3 supplementation can provide benefits for neuroprotective and antiepileptic functions, as well as reduce inflammation that may lead to recurrent seizures in epilepsy patients. Omega-3 doses can be given in adults and children in low doses of around 1200 mg of fish oil per day (240 mg EPA and 360 mg DHA) to patients for a minimum of 12 weeks to reduce the frequency of seizures. Further research is different methodologies and designs to prove the benefits of the administration of omega-3 in patients with recurrent epileptic seizures.

## Conflict of interest

The authors declare that they have no competing interests.

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## ORIGINAL PAPER

## Effect of smartphone application with reminder on total fluid intake adequacy and hydration status among adults in Bontang, East Kalimantan

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### Abstract

**Background:** About 41% adults in Kalimantan have inadequate total fluid intake (TFI), which is higher than national inadequacy (28%). Inadequate TFI may cause dehydration. The biggest barrier to comply with TFI is to forget to drink. Smartphone application, Hidrasiku with reminder, is expected to be useful in TFI adequacy which may affect hydration status.

**Objective:** This study aims to determine the effect of the Hidrasiku with reminder on the TFI adequacy and hydration status among adults in Bontang.

**Methods:** The design of this study was quasi-experimental and cluster sampling. Inclusion criteria were healthy men, age 19-64 years and having a smartphone. Participants suffering with diseases that affected fluid balance and on diet and fluid restriction were excluded. Data collection was conducted from April to June 2023 in Bontang. A total of 106 participants were allocated into two groups, intervention and control. Both groups used Hidrasiku for four weeks, with the intervention group activating the reminder while the control group didn't. Adequacy of TFI and hydration status were assessed before-after intervention.

**Results:** A sample of 87 participants completed the study. The median age of the participants was 32 (19-61) years. At the end of intervention, there was significant difference in the TFI adequacy (90.2% vs 63.0%;  $p=0.003$ ) and a significant increase in TFI +240 mL/day vs -62.8 mL/day;  $p=0.002$ ). Meanwhile no significant difference on hydration status (87.8% vs 73.9%;  $p=0.103$ ).

**Conclusions:** Hidrasiku with reminder has effect on the TFI adequacy and no effect on hydration status

**Keywords:** adult, fluid intake, hydration status, reminder, smartphone

### Introduction

The balance between fluid intake and output reflects hydration status.<sup>1,2</sup> Adequate total fluid intake (TFI) is essential for maintaining the health and functionality of the human body. Insufficient

TFI may cause dehydration. Dehydration may affect human health even cause death.<sup>3</sup> Mild dehydration can have negative impacts, including headache, irritability, decreased physical performance, and impaired cognitive function.<sup>2,4,5</sup> Acute or chronic dehydration may affect urological, gastrointestinal, circulatory, neurological, and metabolic disorder.<sup>1,3,6,7</sup>

Total fluid intake (TFI) for Indonesian adults was  $2,721 \pm 22$  mL/day and met the Indonesian

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recommendation on adequate intake.<sup>8,9</sup> However, about 28% of adults had insufficient TFI. The three regions with the highest rate of insufficient daily fluid intake were Bali (42 %), West Java (42%), and Kalimantan (41%). The study also showed that only 67% of men met the recommended daily fluid intake, which was lower than women (75%).<sup>8</sup> From 13 countries, about 40.6% of men complied with TFI recommendation, while 59.2% of women adhered to TFI recommendation.<sup>10</sup>

There were several barriers to comply TFI: not feeling thirsty, forget to drink, and not having time to drink. About 60% of subjects forgot to drink and ignored the importance of fluid intake.<sup>11</sup> Patients with a history of kidney stones used various methods as reminders to increase fluid intake to prevent recurrence of kidney stones but were unable to accurately monitor daily fluid intake.<sup>12</sup> The use of technology can overcome barriers and provide reminders for patients to adhere TFI recommendations. Application, smart water bottle, and wearable devices can be used to change behaviour to meet fluid intake.<sup>13</sup> Smartphone applications provide useful programs for users to monitor fluid intake, with most of them providing reminders to users, sharing facilities, educational materials, and motivation related to their drinking behaviour.<sup>14,15</sup> Having a reminder in the application is important for dealing with subjects who have difficulty remembering their fluid intake goals or have difficulty tracking their fluid consumption.<sup>16</sup>

The Indonesian Hydration Working Group (IHWG) developed Hidrasiku, an application designed to calculate daily fluid needs, track fluid intake, remind users to drink, and provide education regarding hydration.<sup>17</sup> There have been no trials in healthy adults to evaluate the efficacy of applications related to fluid intake and hydration.<sup>18</sup> Hydration-related applications provided little information about the importance of hydration and did not use other hydration measures, such as physical activity level, urine volume, or urine colour.<sup>14</sup> The effect of Hidrasiku with reminder to TFI adequacy and hydration status using urine colour was unknown. Bontang is located in Kalimantan, the region where

insufficient TFI is higher than national.<sup>8</sup> Men were chosen because TFI adequacy was lower than women.<sup>8,10</sup> The study conducted for four weeks because from the previous study there were needed three to twelve weeks to change the behaviour to increase water intake.<sup>11,16,19</sup> Therefore, the purpose of this study was to determine the effect of Hidrasiku with reminder on TFI adequacy and hydration status among adults in Bontang, East Kalimantan.

## Methods

This study used a quasi-experimental research design to assess the effect of the Hidrasiku with reminder on TFI adequacy and hydration status. The data collection was conducted from April 2023 to June 2023 in Bontang. The inclusion criteria were men, aged 19-64 years, healthy based on a physical examination conducted by a doctor, owning a smartphone, being able to read and write, and signing informed consent. The exclusion criteria were participants who suffered with diseases that affected fluid balance (urinary tract infections, kidney disorders, hypertension, diabetes, heart disease) and on diet and fluid restriction.<sup>20,21</sup> The dropout criteria were participants who suddenly had disease that affected fluid balance, refused to continue, and refused to do end line measurement. A sample size of 50 participants was determined for each group, including the possibility of missing data and a drop-out rate of 20%.<sup>22</sup>

We conducted cluster sampling using secondary data from non-communicable disease screening results at public health centres in Bontang Utara and Bontang Selatan. Researchers and health cadres from public health centres contacted participants who met the criteria and were willing to participate in the study until the number of participants was met. Then, the researcher went on a home visit to collect data. In this study, participants who met the inclusion criteria were 1,420 men. Participants who signed the informed consent were 106 people.

Participants were allocated to two groups, intervention group (IG) and the control group (CG). Both groups used Hidrasiku for four weeks,

with the intervention group activating the reminder to drink every 2 hours from 06.00 a.m. to 10.00 p.m., while the control group didn't. This reminder to fulfil the recommendation to drink water eight glasses a day.<sup>9</sup> As baseline data, interviews were conducted to obtain data on participants' sociodemographic characteristics. Physical activity was assessed using the International Physical Activity Questionnaire-short form.<sup>23</sup> Anthropometric examination was carried out according to standards.<sup>24</sup> TFI was recorded using a 7-day fluid record with Hidrasiku. Participants sent a screenshot from the result of Hidrasiku at 10.00 p.m. daily because the data could not be retrieved directly from the server.  $TFI \geq 2,000$  ml/day categorized as adequate.<sup>25</sup> Participants were examined for urine colour on Saturday by collecting urine taken at 2.00 p.m. – 8.00 p.m.<sup>26</sup> This study evaluated urine colour using the eight-shade urine colour scale published by Armstrong. A transparent urine collection container was placed against a plain white background in a well-lit room.<sup>27</sup> Participants took a photo of it and sent it to the researchers by WhatsApp. For four weeks, the participants recorded their fluid intake in Hidrasiku and examined urine colour weekly with same procedure as before intervention. Participants received education about the importance of fluid intake for health every week. Participants' adherence was assessed by counting the number of days in which participants recorded TFI with Hidrasiku. Participants were considered to adhere if recorded TFI in Hidrasiku 4-7 days in a week. The adherence score calculated from adherence in four weeks. Data collection began after obtaining approval from the Research Ethics Committee of Faculty of Medicine Universitas Indonesia number KET-438/UN2.F1/ETIK/PPM.00.02/2023.

Participants who reported TFI below 0.4 L/day or higher than 6 L/day were excluded from the analysis.<sup>8,25</sup> Data were analysed using Statistical Package for Social Science (SPSS) software version 26.0. All data were analysed descriptively. Numerical data were analysed using the Kolmogorov-Smirnoff or Shapiro Wilk for normality test. Statistical analysis for

numerical data was analysed by unpaired t test or Mann-Whitney. Meanwhile, categorical data were analysed using Chi-square or Fischer test. The before-after in TFI adequacy and hydration status within one group were tested using the McNemar test. The change in TFI between two groups was analysed by unpaired t test or Mann-Whitney. The before-after TFI within one group were tested by paired t or Wilcoxon. The significance level was set at  $p < 0.05$ .

## Result

A sample of 87 participants completed the study. The characteristics of the participants are shown in **Table 1**. The median age of the participants was 32 (19-61). About 52.9% participants were obese. Most of the participants in both groups had a job and high level of education. Most of the participants' physical activity was moderate level. TFI for all participants' ( $n=87$ ) was  $2,216.0 \pm 433.4$  mL/day. The median of urine colour was 3 (1-7).

TFI adequacy of all participants at baseline were 69.0%. TFI adequacy at baseline in IG was higher than CG (70.7% vs 67.4%;  $p=0.737$ ). At the end of the study, the TFI adequacy of all participants were 75.9%. There was an increase in the TFI adequacy in IG at the end of intervention while in CG there was a decrease in the TFI adequacy (90.2% vs 63.0%;  $p=0.003$ ). There was a difference in changes in the TFI adequacy before and after treatment in IG ( $p=0.021$ ) while in CG was not ( $p=0.774$ ).

To find out the changes before and after treatment in the two groups, the researchers added the effect of Hidrasiku on TFI. At baseline, TFI in the two groups was not significantly different ( $p>0.05$ ). At the end of the treatment, there were significant differences and changes in the two groups ( $p<0.05$ ).

At the baseline, 66 participants (75.9%) were categorized in euhydration. The euhydration status of IG was lower than CG (75.6% vs 76.1%;  $p=0.959$ ). After four weeks of intervention, there was an increase in euhydration status in IG while

**Table 1.** Participants' Characteristic

Variable	Intervention (IG) (n=41)	Control (CG) (n=46)	P value
Age (years)*	33 (19–55)	31.5 (19–61)	0.369 <sup>MW</sup>
Nutritional status, n (%)			0.665 <sup>f</sup>
Underweight	2 (4.9)	5 (10.9)	
Normal	9 (22)	11 (23.9)	
Overweight	6 (14.6)	8 (17.4)	
Obese	24 (58.5)	22 (47.8)	
Education level, n (%)			0.435 <sup>f</sup>
Low	1 (2.4)	0 (0)	
Middle	16 (39)	22 (47.8)	
High	24 (58.5)	24 (52.2)	
Job status, n (%)			0.255 <sup>f</sup>
Un-employee	0 (0)	3 (6.5)	
Retired	0 (0)	1 (2.2)	
College student	1 (2.4)	2 (4.3)	
Employee	40 (97.6)	40 (87.0)	
Physical activity level, n (%)			0.193 <sup>CS</sup>
Low	7 (17.1)	11 (23.9)	
Moderate	20 (48.8)	27 (58.7)	
High	14 (34.1)	8 (17.4)	
TFI (mL/day)**	2,191.3 ± 372.7	2,238.0 ± 484.1	0.619 <sup>t</sup>
Urine colour*	3 (1-6)	3 (1-7)	0.914 <sup>MW</sup>

Notes:

IG: Intervention Group

CG: Control Group

\*Median (minimum-maximum)

\*\*Mean ± standard deviation

<sup>MW</sup>: mann-whitney test; <sup>f</sup>: Fischer test; <sup>CS</sup>: chi-square test; <sup>t</sup>: unpaired t test**Tabel 2.** Effect Hidrasiku on TFI

Variable	IG (n=41)	CG (n=46)	P value
<b>TFI (mL/day)</b>			
Baseline	2,191.3 ± 372.7	2,238.0 ± 484.1	0.619 <sup>t</sup>
End line	2,285.7 (1,458.3–3,792.9)	2,110.0 (1,348.6–3,490.0)	0.014 <sup>MW</sup>
P value before- after intervention	0.002 <sup>W</sup>	0.240 <sup>W</sup>	
Δ (mL/day)	240 (-467.9–1,214.3)	-62.8 ± 458.4	0.002 <sup>MW</sup>

<sup>t</sup>: unpaired t test; <sup>MW</sup>: mann-whitney; <sup>W</sup>: wilcoxon.

there was a decrease in CG (87.8% vs 73.9%;  $p=0.103$ ). However, no significant differences were found at the end of the treatment in the two groups, before and after treatment ( $p>0.05$ ).

The participants' adherence in IG was higher than CG (97.6% vs 93.5%). There was no significant difference between the two groups ( $p=0.619$ ).

## Discussion

In the present result, the mean of TFI for all participants' ( $n=87$ ) was  $2,216.0 \pm 433.4$  mL/day. Participants on IG had a TFI of  $2,191.3 \pm 372.7$  mL/day, while those on CG had a TFI  $2,238.0 \pm 433.4$  mL/day. This amount of TFI was similar from the national survey which was conducted in 2016 for Kalimantan,  $2,208 \pm 45$  mL. However, it was still lower than the national TFI average of  $2,721 \pm 22$  mL.<sup>8</sup> These rates were similar from other previous data from Indonesia  $2,280$  mL ±

1,020.<sup>10</sup> But these results were higher than Indonesian Total Diet Study in 2014 which reported 1,317 ml/day.<sup>28</sup>

Prior to intervention, 68.6% of participants met the recommended TFI. This value was higher than previous study, 67% of Indonesian men met the adequacy of TFI.<sup>8</sup> This value was also higher when compared to a study conducted in Germany where 66% of men participants adhere with TFI recommendation.<sup>10</sup> TFI adequacy for IG was higher than CG (70.7% vs 67.4%). This value was higher when compared TFI adequacy in Kalimantan, 59%.<sup>8</sup> The need of TFI to each individual is different, influenced by age, gender, body mass index (BMI), physical activity and environment.<sup>1,2,29</sup>

Hydration status based on the urine colour chart before intervention showed that 76.7% of the participants were hydrated and 23.3% were dehydrated. The euhydration status of IG was higher than that of CG. Study in Yogyakarta showed that 60.9% of students in university were dehydrated.<sup>30</sup> Another study on workers in Surabaya showed that 85.71% of participants were minimally dehydrated and 14.29% of participants were significantly dehydrated.<sup>31</sup> The plasma osmolality will rise and stimulate osmoreceptors in the hypothalamus if the body loses more water than intakes. Antidiuretic hormone will be released and cause increasing water reabsorption in the kidneys. So that urine excretion will decrease and urine will be more concentrated and become a darker colour.<sup>32</sup>

After 4 weeks, the TFI adequacy increased significantly in IG while CG decreased. The main barrier in adhering TFI adequacy was forgetting to drink.<sup>11,12</sup> The use of an application with reminder is suitable for patients who have difficulty remembering their fluid intake goals or have difficulty tracking their fluid consumption throughout the day.<sup>18</sup> Reminder is implemented as periodic messages which is sent to the user reminding them to check out the application. Daily or weekly reminders were sent to encourage users to continue using the application.<sup>33</sup> Reminders will be sent to users who do not reach the user's target to maintain motivation.<sup>34</sup> TFI increased in users' application

after enabling the reminder feature. However, when the reminder was turned off, TFI returned to baseline. This study shows that reminders were useful in health management. However, participants were unable to sustain these changes when the reminder was turned off.<sup>16</sup> Another study reported a greater increase in 24-hour urine volume and decreased the difficulty remembering to drink with the use of smart drinking bottles.<sup>11</sup> A further study reported that using a drinking reminder application in nephrolithiasis patients, twenty-nine percent of patients achieved the goal of daily urine output volume >2.5L across all treatment groups ( $p < 0.001$ ).<sup>35</sup> The key to behaviour change is self-management, which is related to the active participation of an individual in terms of treatment or in maintaining health. This includes goal setting and action planning in achieving goals in health.<sup>36</sup>

For the hydration status, IG tended to experience a change in hydration status to euhydration in the end line. However, the change was not statistically significant between the two groups. Hydration status is influenced by several factors such as age, sex, BMI, physical activity, environment, and disease.<sup>1,2,29</sup> Individuals who are obese have a higher need for water than individuals who are not. Water needs depend on their metabolic rate, body surface area, and body weight.<sup>29</sup> The average respiratory water loss in a person with high physical activity can reach 500 to 600 mL/day. Meanwhile, when exercising, up to 1.5 L of water loss through sweat can occur when exercise for a long time and in a hot environment.<sup>3</sup> If it is not replaced with sufficient water consumption, it will cause a deficit of body water and may affect hydration status.<sup>1-3</sup> It is possible that there was no difference after intervention in both groups because they have the same drinking target, 2 L according to the Indonesian recommendation on adequate intake without considering BMI, physical activity, and environment. Most of the participants were obese and had a moderate level of activity. Even though the participants in IG and CG had met their TFI in the application, if on the day of the urine colour examination, the participants were

active and the weather was hot as a result, it might affect the results of the urine colour examination.

With the reminder, IG's adherence in recording TFI in Hidrasiku was higher than CG's. However, this difference was not statistically significant. This was due to the possibility that the adherence of the two groups reached > 80%, where it was the limit to adhere with the recommendations.<sup>37</sup> In addition, the researchers sent reminders to the participants every day at 9.00 p.m. to ask the participants to send the results of Hidrasiku at 10.00 p.m. because the results of the recording cannot be directly retrieved from the server. This was expected to affect the high level of participants' adherence so that the results do not differ significantly between both groups.

This study has several strengths; this study is the first to be conducted in Indonesia. Then as a preliminary study, the number of samples meets the expected number of samples. Most of the participants adhere to intervention. This study also has some limitations. Neither participants nor researchers were blinded so there was a risk of bias. Then, the data recorded in the application cannot be retrieved directly from the server. There was a problem where the application wasn't showing any data because many users opened the application simultaneously. When the application could show the data, the participants tried to input the data and they were informed that the data had failed to be registered. So, the participants tried several times to input it again. But in fact, the data had been successfully registered, and they unintentionally input the same data multiple times. In addition, the application did not limit the number of intakes that could be recorded in one input. One participant reported not intentionally input 10,000 mL and no prior warning if the amount was too large. The reminder in the application sometimes didn't provide data that matches the user's last intake. Urine colour examination was carried out by sending a photo of the urine sample alongside the urine colour chart which has the risk of giving different results due to lighting. Previously, participants had been taught to check urine colour results with a urine

colour chart, so the researchers might confirm the urine colour results with the participants.

## Conclusions

Hidrasiku with reminder has an effect on TFI adequacy. However, it has no effect on hydration status. Hidrasiku with reminder can be used to promote TFI adequacy for adults because it can reduce common barriers to adhere with TFI recommendation. Application development can consider the reminder as default from the application, limit the amount of intake that can be recorded in a certain time, consider body weight, physical activity level, environment in determining daily fluid requirements, and upgrade servers so that it can be used by many people. Further research is needed regarding user acceptance and satisfaction with Hidrasiku

## Declaration of interest

The authors declare that no conflict of interest with another person or institution.

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## ORIGINAL PAPER

## The association between knowledge and attitude towards nutrition fact panels (NFP) with sugar intake of the Indonesian adolescents

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### Abstract

The increasing sugar intake has become a global issue due to its impact on health. The survey conducted in Jakarta revealed that the median sugar intake for adolescents and adults is 18.8 g/capital/day and 24.5 g/capital/day, respectively. The government has taken several ways to reduce sugar intake, one of which is by using labels on packaged food. Therefore, this research aims to investigate the knowledge and attitude towards nutrition fact panels with sugar intake in Indonesian adolescent. This research was a cross-sectional study using an online questionnaire for adolescents in Indonesia with age range between 15-18 years old. Data on sociodemographic, mass media exposure, knowledge, and attitude were collected through online questionnaires, while sugar intake was assessed through online SQ-FFQ interviews. The study's findings showed that the majority of respondents were women (90%), with parents having below 12 years of schooling on average. Additionally, the median monthly pocket money and pocket money for food and drinks below IDR 300,000 and IDR 200,000, and mass media exposure occurred more than 3 times per month. More than half of the respondents displayed good knowledge (51.7%) and a positive attitude towards NFP (60.8%), with the majority having high sugar intake (53.5%). There is a relationship between knowledge of NFP, mass media exposure, and mother education with sugar intake in adolescents. It recommended to enhance knowledge of NFP among adolescents and parents through social media platforms, posters and TV ads to enable them select and consume appropriate foods.

**Keywords:** adolescents, attitude, nutrition knowledge, nutrition fact panels, sugar

### Introduction

The issue of increased sugar consumption is a global concern, as it has been associated with various health problems.<sup>1</sup> In addition, the consumption of packaged foods and beverages,

including sugar-sweetened beverages has been on the rise.<sup>2</sup> According to Food and Agriculture Organization (FAO) forecast for world sugar production in 2021/22 (October/September) is pegged at 174.6 million tonnes, up 5.1 million tonnes (3 percent) from the reduced level of 2020/21.<sup>3</sup> The highest per capita sugar consumption is in Europe, where the average person consumes around 33 kg of sugar per year.<sup>4</sup> Indonesia is ranked as the third-largest consumer of sugar in Asia, following India and China.<sup>5</sup>

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Data from Total Diet Survey in 2013 indicates that 4.8%, 18.3%, and 26.5% of the Indonesian population's consumption of sugar, salt, and fat has exceeded the recommended daily limits set by the Minister of Health, which are 50 grams of sugar, 2000 mg of sodium, and 67 grams of fat per person a day.<sup>6</sup> Several smaller studies showed that the consumption of sugar has increased ever since. A survey in Jakarta showed that the median sugar intake of adolescents and adults is 18.8 g/capital/day and 24.5 g/capital/day and the major contributor was sugar-sweetened beverages.<sup>7</sup>

As we are aware, poor eating habits, which involve high sugar consumption, have been identified as contributing factors to a decline in average life expectancy and are closely linked to various health conditions. The excessive consumption of free sugars leads to an overall increase in energy intake and may result in reduced consumption of nutritionally dense foods, thereby being associated with numerous detrimental health outcomes.<sup>8</sup> Evidence indicates a strong correlation between the substantial increase in obesity rates and the consumption of sugary beverages, which in turn has led to a rise in chronic diseases. Numerous studies have established a link between excessive consumption of sugary drinks and both obesity and an increased risk of various chronic diseases. Among different population groups, children and adolescents are particularly susceptible to the harmful effects of sugary beverages. In comparison to other age groups, children, and adolescents consume a higher proportion of their total caloric intake in the form of sugars.<sup>9</sup>

One of the strategies employed to reduce sugar consumption was through the provision of nutrition information on the label of packaged or processed food.<sup>10</sup> Other strategies implemented in several countries such as New Zealand, the United States, Mexico, France, and others to reduce sugar intake, particularly the limitation of sugar-sweetened beverage (SSB) consumption, include measures such as price adjustments, heightened public awareness, restrictions on SSB availability, and promotion of healthier beverage options.<sup>9</sup> Food labelling aims to provide accurate and clear information to the public about packaged food

products prior to purchase and/or consumption. In a systematic review and meta-analysis of 60 studies, comprising 111 intervention arms and over 2 million observations conducted across 11 countries, the findings indicate that food labelling has been effective in reducing consumer consumption of total energy and total fat, while simultaneously increasing vegetable consumption.<sup>11</sup> In the past two decades, various types of food labelling have been developed with the initial efforts focusing mostly on packaged food, for example, nutrition fact panels, menu calorie labels, traffic light labels, logos such as :”keyhole”, “choice”, and “health-check”, and nutrition-or health-related claims.<sup>11</sup> In Indonesia, the inclusion of a nutritional fact panel on packaged or processed food labels was mandatory since 2021.

However, a study revealed that the utilization of nutrition labels did not demonstrate a significant association with healthier dietary patterns among adolescents. Although adolescents commonly utilized nutrition labels, their primary focus seemed to be on expiration dates rather than the nutritional information provided. Findings from the National Health and Nutrition Examination Survey (NHANES) data indicated that the adoption of nutrition labels among adolescents is relatively low.<sup>12</sup>

There are various factors that may influence individuals' propensity to utilize and peruse food labels, including age, income, education, gender, employment status, health status, knowledge of nutrition and food labels, parents' income and the importance of flavour and nutrients. Knowledge plays a crucial role in shaping individuals' thoughts and behaviors, including their reading habits and attention to nutritional information on food labels.<sup>13</sup> Another study found that individuals with higher levels of nutrition knowledge were 17.7 times more likely to read the nutritional information on food packaging.<sup>14</sup> Furthermore, research by Acheamong and Haldeman<sup>15</sup> suggests that consumers with better nutrition knowledge tend to have a good attitude toward healthy eating. Previous findings also have shown that NFP use is associated with reduced sugar and total cholesterol

intake, as well as increased fiber, vitamin C, and iron intake.<sup>15,16</sup>

A study revealed that the utilization of nutrition labels did not demonstrate a significant association

with healthier dietary patterns among adolescents. Although adolescents commonly utilized nutrition labels, their primary focus seemed to be on expiration dates rather than the nutritional information provided.<sup>17</sup> Findings from the National Health and Nutrition Examination Survey (NHANES) data indicated that the adoption of nutrition labels among adolescents is relatively low.<sup>18</sup> Another study conducted among university students in Jakarta indicated that there was no correlation between the use of Nutrition Fact Panels (NFP) and overall diet quality.<sup>17</sup> It can be concluded that no studies have examined the association between the knowledge and practice of Nutrition Fact Panels (NFP) and sugar consumption among adolescents.

The researchers aim to investigate the knowledge and attitudes of adolescents on the Nutrition Fact Panels (NFP) and its association with sugar consumption. This study could provide valuable insights for developing preventive strategies to promote healthier dietary choices among adolescents.

## Methods

### *Design, location, and time*

The research was performed on Indonesian adolescents aged between 15 and 18 years who had completed junior high school. It was designed as a cross-sectional study and was carried out online between July and September of 2022. Before commencing data collection, the Ethical Committee of the Faculty of Medicine at Universitas Indonesia approved the study (KET.461/UN2.F1/ETIK/PPM.00.02/2022).

### *Sampling*

The population of the study was adolescents aged 15-18 years old in Indonesia who have access to an online survey. To be included in the study,

participants needed to be Indonesian citizens aged between 15 and 18 years old, have completed junior high school, and have internet access and the ability to use it. Those who had serious medical conditions like chronic infectious diseases, chronic diarrhea, or were undergoing medication or diet therapies, as well as those with special needs who were unable to communicate normally during the interview or use the internet, were excluded from the study.

Sample Size was calculated to estimate an association between knowledge and sugar intake based on the previous study with 95% confidence interval. Based on a previous study indicating a correlation value  $r = 0.43$  between knowledge and sugar intake, as well as attitude and sugar intake.<sup>19,20</sup> However, given the absence of a link between NFP usage and diet quality in other research, we opted for a more conservative approach to the association and estimated the sample size using  $r = 0.3$ .<sup>17</sup> Based on these calculations, the minimal sample size needed was 85. As this study was conducted online, we factored in a response rate of 30% from the prior study, resulting in a total of 110 individuals for the analysis.

Study participants were recruited voluntarily by disseminating research-related information through various social media platforms such as the internet, WhatsApp, and Instagram. This study employs quota sampling to select participants. Interested individuals are given the opportunity to pre-register until the desired sample size is attained. Upon completion of the registration process, the respondents will be contacted for an interview to complete the SQ-FFQ questionnaire.

### *Data collection*

The study's eligible participants were contacted by the researcher or enumerator and provided with an informed consent form along with a survey link that covered socioeconomic characteristics, mass media exposure, knowledge, and attitude toward NFP. Upon completion of the survey link, the enumerator contacted each respondent to conduct an SQ-FFQ interview.

Prior to the study's commencement, the questionnaire underwent a pre-testing process to evaluate the understanding, estimate the time required for its completion, ensure a seamless interview process, and address any logistical or potential issues.

The knowledge questionnaire used has been previously used and assessed.<sup>17</sup> Assessment of internal reliability of knowledge was among 30, a Cronbach's alpha coefficient of 0.73. The current study's nutrition knowledge covered four topics: dietary recommendation (four questions), sources of nutrients (five questions), diet-disease relationships (four questions), and understanding of the Nutrition Facts Panel (ten questions).<sup>17</sup>

The questionnaire used to assess attitudes towards Nutrition Fact Panels (NFP) was also been previously used.<sup>21</sup> The pretest results of the attitude questions yielded a Cronbach's alpha coefficient of 0.605. Participants responded to nine questions designed to assess their perceptions of the NFP label, using a Likert scale ranging from strongly disagree (1) to strongly agree (4).

Sugar intake in this study was assessed using SQ-FFQ, which is specifically designed for assessing sugar intake in adolescents.<sup>22</sup> This form had been previously developed and validated in a prior study. The SQFFQ form demonstrated high reliability with strong agreement between the two administrations, which were conducted one month apart. The results of relative validity, utilizing 6-day food diaries as the reference method, showed a remarkable capability to precisely rank individuals into the same and adjacent categories, with less than 10% gross misclassification in all sugar intake assessments. The questionnaire included a total of 49 food ingredients, which were categorized into six groups: carbohydrates sources, sugary packaged food, sweet snacks, packaged drinks, fruit and additional sugar food. Sixteen options were provided in the category for frequency of intake, ranging from never to more than three times a day.<sup>22</sup>

In this study, various food composition databases were utilized to calculate the total sugar intake derived from the consumption of food and

beverages by the participants. The database employed encompassed the Indonesian food composition database, the Malaysian food composition database, the Filipino food composition database and the USDA food data center. The sugar content of packaged meals or beverages was determined by checking the nutritional information provided on the packaging. Based on the provided nutritional information, the total sugar intake was calculated considering both the frequency and amount of consumption reported by respondents over the last month. For each food and beverage category, the total sugar content was computed, and the individual results were aggregated to determine the daily total sugar intake of each respondent.

### *Data analysis*

The data analysis was carried out using SPSS for Windows version 20.0. Descriptive numerical data were presented using descriptive statistics such as mean, standard deviation or median, while categorical data were presented as percentages. The association between knowledge and attitude towards NFP as well as mass media exposure score and the level of sugar intake was analyzed using Spearman's test, while the relationship between sugar intake and socio-demographic characteristics was analyzed using the Mann-Whitney test. Furthermore, variables that showed a p-value < 0.2 in the bivariate analysis were included in the multiple linear regression test to evaluate their relationship with sugar intake after controlling for potential confounders.

## **Results**

### *Socioeconomic and demographic characteristics*

The total number of respondents who have completed this research phase was 120 respondents. **Table 1** presented the general characteristics of respondents. The respondents' median age in regard to sociodemographic factors was 17 years old. The majority of participants were females (90%) while the rest were males (10%). The majority of parents' education was



less than 12 schooling years, 60% for the father’s education and 60.8% for the mother’s education. The average monthly value of pocket money and pocket money for food and drink was IDR 300,000 and IDR 200,000, respectively. The group of respondents who fall below the median cut-off includes more than half of them (52.5% for pocket money and 65% for pocket money for food and drink). Furthermore, the data indicates that the respondents are exposed to media at various frequencies, ranging from 1 to more than 3 times per month.

**Table 1.** Socioeconomic demographic characteristics of respondents (n=120)

Variable	Median (min-max)	(%)
Age	17 (15 – 18)	
Gender		
Men		10%
Women		90%
Father Education		
Less or equal than 12 schooling years		60%
More than 12 schooling years		40%
Mother Education		
Less or equal than 12 schooling years		60.8%
More than 12 schooling years		39.2%
Pocket money for a month		
Less or equal median IDR 300.000		52.5%
More than the median IDR 300.000		47.5%
Pocket money for food and drink for a month		
Less or equal median IDR 200.000		65%
More than the median IDR 200.000		35%
Mass media exposure	14 (10 – 23)	

*The median score of media exposure indicates that the larger value, the higher frequency of respondents being exposed to mass media, more than 3 times per month. This score obtained from the sum of several statements reflecting how often an individual is exposed to information within a month.*

IDR : Indonesian Rupiah

In **Table 2**, it was found that over half of respondents possessed good knowledge (51.7%) and good attitudes (60.8%) towards nutrition facts panels. Moreover, the respondents had a higher sugar intake, which was more than half of the total

(52.5%). **Figure 1** indicates that the beverage group was the most consumed food group containing sugar among teenagers. Moreover, following the beverage group, other frequently consumed food group include the additional sugar food group and sweet snacks group.

*Association between sociodemographic, knowledge and attitude with sugar intake*

The main objective of this study was to assess the association between knowledge, attitude of NFP and sugar intake in adolescent. **Table 3** presented the association of sociodemographic variables, including gender, age, parent’s education, pocket money for a month, pocket money for food and drinks for a month, mass media exposure with sugar intake. The results indicate that two variables, namely mother

**Table 2.** Distribution of knowledge, attitude, and sugar intake of respondents (n=12)

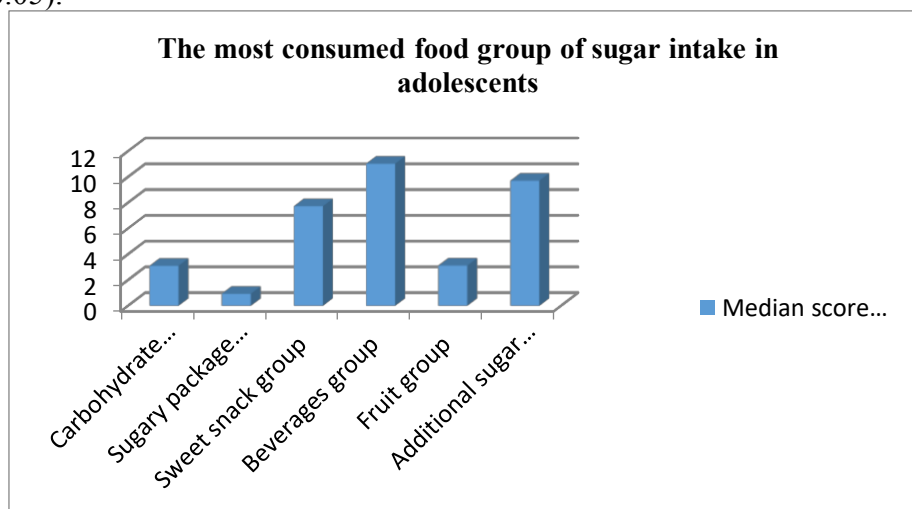
Variable	Median (min-max)	(%)
Knowledge of NFP	14 (0 – 21)	
Not good knowledge < 14		48.3%
Good knowledge ≥ 14		51.7%
Attitude of NFP	25 (20 – 31)	
Not good attitude < 25		39.2%
Good attitude ≥ 25		60.8%
Sugar Intake	50.92 (33.10 – 76.33)	
High sugar intake ≥ 50 gr/days		52.5%
Adequate sugar intake < 50 gr/days		47.5%

education and mass media exposure, had a significant relationship with sugar intake in adolescents ( $p<0.05$ ).

In order to explore the association between knowledge and attitude towards NFP and sugar consumption, the Spearman test was employed, **Table 4** illustrates that there is a significant relationship between knowledge with sugar intake in adolescents ( $p<0.05$ ). However, there is no



relationship between attitude with sugar intake in adolescents ( $p < 0.05$ ).



**Figure 1.** Detail analysis of food group of sugar intake in adolescents (gram)

**Table 3.** Association between sociodemographic with sugar intake

Variable	Sugar intake	R	p-value
	Median (min – max)		
<b>Gender</b>			
Men	56.40 (27.93 - 210.85)		0.319 <sup>1</sup>
Women	50.53 (11.55 - 210.10)		
<b>Age</b>		-0.122	0.184 <sup>2</sup>
<b>Father Education</b>			
Less or equal than 12 schooling years	49.54 (11.55 – 210.85)		0.371 <sup>1</sup>
More than 12 schooling years	52.61 (13.66 – 290.10)		
<b>Mother Education</b>			
Less or equal than 12 schooling years	41.95 (11.55 – 197.49)		0.007 <sup>1*</sup>
More than 12 schooling years	63.26 (15.85 – 290/10)		
<b>Pocket money for a month</b>			
Less or equal median IDR 300.000	43.75 (11.55 - 145.49)		0.402 <sup>1</sup>
More than median IDR 300.000	55.23 (13.66 - 290.10)		
<b>Pocket money for food and drink for a month</b>			
Less or equal median IDR 200.000	43.06 (11.5 - 210.85)		0.172 <sup>1</sup>
More than median IDR 200.000	59.61 (19.23 - 290.10)		
<b>Mass media exposure</b>	59.61 (19.23 – 290.10)	0.177	0.053 <sup>2*</sup>

Note : 1 Mann Whitney U test analysis

2 Spearman test analysis

\*Significant level  $p < 0.05$

**Table 4.** Association between knowledge and attitude with sugar intake

Variable	Sugar intake	R	p – value
	Median (min – max)		
<b>Knowledge of NFP</b>			
Not good knowledge	60.22 (15.87 – 197.49)	-(0.176)	0.023 <sup>1*</sup>
Good knowledge	39.45 (11.55 – 290.10)		
<b>Attitude of NFP</b>			
Not good attitude	49.34 (16.24 – 164.56)	0.049	0.709 <sup>1</sup>
Good attitude	51.04 (11.55 – 290.10)		

**Table 5.** Multivariate Analysis of several variables associated to sugar intake in adolescents

Variable	Unadjusted			Adjusted		
	B	Standard error	p-value	B	Standard error	p-value
Age	-2.011	3.752	0.593	0.546	3.734	0.884
Mother education	21.686	8.008	0.008	22.548	8.223	0.007*
Pocket money for food and drink for a month	7.936	8.414	0.348	11.669	8.275	0.161
Mass media exposure	2.319	1.376	0.095	1.683	1.362	0.219
Knowledge of NFP	-8.513	8.023	0.291	-1.696	1.169	0.150

As an additional study, multiple regression analysis in **Table 5** was performed to assess the correlation between knowledge and attitude of NFP and sugar intake while adjusting for potential confounding factors such as age, mother’s education, pocket money for food and drink, media exposure, and knowledge of NFP. The findings revealed that after controlling for potential confounders, the mother’s education significantly contributed to sugar intake in adolescents compared to other potential confounding factors ( $\beta = 22.54$ ,  $p < 0.05$ ).

**Discussion**

In the present study, the median age of the respondents was 17 years, indicating that the majority of the sample comprised middle adolescents who possess a higher level of maturity and autonomy to make their own decisions.<sup>23</sup> Additionally, the majority of the participants’ parents had attained no more than 12

years of education, equivalent to a maximum of high school education. According to the 2022 SUSENAS, out of 100 Indonesian residents aged 15 years and above, 22 have completed junior high school education, 29 people have graduated from high school, and 10 have completed tertiary education.<sup>24</sup> This indicates that the average Indonesian has a high school level of education. In 2020 SUSENAS data also showed that the average woman in Indonesia is up to senior high school.<sup>25</sup> Adolescents with mothers having lower levels of education reported higher availability of unhealthy food at home than mothers with higher education levels and were more likely to restrict their children’s consumption of harmful food such as sweets, soft drinks, and chips.<sup>26</sup>

The amount of pocket money provided can have an impact on the type and selection of food consumed by adolescents, particularly packaged food. As a result, pocket money can indirectly influence the exposure of youths to food labels on packaged foods that are consumed.<sup>27</sup> Another

study revealed that adolescents who received more pocket money consumed packaged food and drinks 12.5% more frequently (more than 3 times a day) in comparison to respondents with lower pocket money (11%).<sup>23</sup> Then the results of the study also show that in the last month adolescents have been exposed to mass media once or twice in the last month. The results of a survey conducted by the Indonesian Internet Service Providers Association (2017) found that internet usage in Indonesia has been increasing year by year. The duration of social media usage per day was found to be 1 – 3 hours (43.89%), 4 – 9 hours (29.63%), and more than 7 hours (26.48%). Based on the detailed research, the respondents were found to be exposed to mass media marketing of extra food and drink products at the supermarket check-out counters. Food purchased at the checkout is typically unplanned, additional purchases that are likely to be driven by impulse. As such, the decision to purchase additional foods may occur subconsciously, making it difficult to suppress, even if the individual does not intend or wish to make such purchases.<sup>28</sup>

#### *Knowledge and attitude of nutritional fact panels in adolescents*

The study findings indicate that the respondents have good knowledge (51.7%) and good attitudes (60.8%) toward Nutrition Fact Panels (NFP). Research conducted by Aritonang<sup>33</sup> regarding sugar, salt and sugar intake showed that respondents had good knowledge (50.2%) and had positive attitudes (58.5%) about sugar, salt and sugar intake in adolescents. Additionally, the results of a previous study demonstrated that individuals with good knowledge tend to read nutrition labels more frequently and exhibit a positive attitude towards reading and comprehending nutrition labels.<sup>29</sup> This highlights the positive relationship between good knowledge and the behavior of reading food labels, which can contribute to the development of healthier dietary habits.

Nonetheless, there are consumers who possess good knowledge yet remain sceptical about the nutritional value information provided on food

labels.<sup>23</sup> The study further emphasizes that respondents who exhibit good attitudes towards food labels are more inclined to read NFP, enabling them to make informed choices while purchasing food items. This is also supported by the research of Ha and Dung<sup>30</sup> which demonstrates that consumers with a positive attitude and stronger support for information on food labels perceive the health benefits of such labels and acknowledge the significance of nutritional information in choosing food products, ultimately motivating them to utilize nutritional value information while making purchases.

#### *Sugar intake in adolescent Indonesia*

Sugar consumption per day in adolescents in this research is still included in the high category (>50 gr/day) (52.5%). The detailed analysis conducted in this research indicates that the food groups most frequently consumed by adolescents that can increase their sugar intake are the beverages group, followed by the additional sugar group and the sugary packaged food group. The results of this study are in line with the findings from the Total Diet Study's 2014 survey, which reported that 56.4% of adolescents aged 15 – 19 years consumed sugar-sweetened beverages (SSB).<sup>31</sup> The findings of the 2018 Basic Health Research (RISKESDAS) indicate that 56.4% of adolescents aged 15 – 19 years in Indonesia consume sweetened beverages more than once a day. On a global level, for example in Malaysia, adolescents consume an average of 1.039 ml/day of sweetened beverages, equivalent to four 250 ml-sized cans.<sup>32</sup> Similar to Indonesia, Korean children and adolescents had higher sugar intake among females (54.3 gr) compared to males (46.6 gr), and another study discovered that the average sugar intake of female Brazilian adults was higher than that of male Brazilian adults.<sup>33,22</sup> According to some of the study's findings, sugar intake in children and adolescents is still in the high category of the recommended limit.<sup>22</sup>

#### *Association between several factors that affect sugar intake in adolescents*

The main objective of this study was to assess the association between knowledge, attitude of NFP and sugar intake in adolescents. In This study indicates that a number of factors, including age, mother and father education, pocket money for month and pocket money for food and drink for month, mass media exposure, knowledge and attitude toward NFP, are related to adolescent sugar consumption. According to the findings of the bivariate test analysis, mother education and mass media exposure are a significant relationship with sugar intake in adolescents. In addition, it is also known that knowledge and sugar intake in adolescents also have a significant relationship, but there is no association between adolescent attitude and sugar intake. However, result from the multivariate analysis showed that mother education has a significant association with sugar intake in adolescent compared to other variables there are age, pocket money for food and drink, mass media and knowledge of NFP.

According to research, respondents with a good level of knowledge are more obedient in reading food labels (57.6%) than respondents with a low level of knowledge (41.4%). The enhancement of skills or knowledge regarding nutritional information can aid in reducing consumer misunderstanding about a food or drink product. A knowledgeable shopper is aware of the food consumed because it is tied to health, therefore desire to read and use food labels increases.<sup>23</sup> Furthermore, adolescents can easily access information from the media because it makes information more accessible especially information regarding nutritional aspects of foods. In the present study found that there is a positive relationship between mass media or media food marketing with increased sugar intake in food. Studies have evaluated print (vending machines, school logos, magazines, or public transportation) or audiovisual (TV) media (observational cross-sectional studies) food marketing exposure and high sugar beverage intake discovered a substantial positive relationship.<sup>34</sup>

Parents are found to play a significant effect in influencing the eating habits of their children by determining which foods are available and how

foods are prepared in the home. One element of the home environment is parental education, and it has been discovered that poorer diets are connected with lower levels of parental education.<sup>35</sup> Research in America shows that parents with low levels of education can significantly increase the consumption of intermediate levels of SSBs aged 2 – 19 years and heavy consumption in adolescents aged 12 – 19 years.<sup>36</sup> Children's and adolescent eating habits have been found to be substantially correlated with parental education level, particularly mother education level.<sup>37</sup> Another research from Guo et al.,<sup>38</sup> stated that the father and mother's low education levels were associated with children's higher SSB consumption (Mantel-Haenszel  $p < 0.01$ ).

This research has limitations as it was conducted with a target audience of adolescents aged between 15 and 18 years. Obtaining respondents within this age range online was not easy task. Moreover, there were some respondents who filled out the online questionnaire but could not be reached for the SQ-FFQ interview. In Addition, conducting online interviews and administering online questionnaires requires a stable data connection. However, some respondents may be difficult to reach for interviews or may encounter issues when completing online forms, necessitating the need for follow up or repeated attempts.

## Conclusion

This study indicates that adolescents possess a good understanding of NFP and exhibit a good attitude towards NFP. However, more than half of the respondents still have a high sugar intake. Additionally, this study reveals an association between knowledge, mass media exposure, and mothers' education with sugar intake among adolescents. On the other hand, attitude does not show a significant relationship with sugar intake among adolescents.

Future nutrition interventions could focus to increase awareness and educate people about NFP, with a particular emphasis on enhancing knowledge about NFP among adolescents and

parents of adolescents. One approach that can be implemented is to emphasize the importance of reading and comparing the nutritional values across multiple NFPs, rather than solely relying on information from a single product label. Additionally, leveraging social media platforms commonly used by teenagers and parents can be effective, such as broadcasting public service advertisements on television, creating short videos for social media platforms or designing posters illustrating how to interpret NFPs. Furthermore, the government can play a role in innovating NFPs by incorporating color-coded indicators that signify whether a product contains a certain level of nutrients categorized as low, medium, or high. This initiative would facilitate understanding and enable parents and adolescents to make informed food choices.

### Conflict of interest

The authors declare that no conflict of interest with another person or institution.

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## Nutrient-rich food index 9.3 score and food choice values among female online food delivery users during COVID-19 pandemic

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### Abstract

**Background:** The COVID-19 pandemic has transformed eating habits, leading to an increased reliance on online food delivery. It's crucial to comprehend the diet quality and food choices among female users during this period.

**Objective:** This study aims to explore the association between diet quality score and the food choice motives among female online food delivery users during the COVID-19 pandemic

**Methods:** This online cross-sectional study involved surveying 405 female users recruited through consecutive sampling. The Food Choice Values Questionnaire (FCVQ) was utilized to understand their food choices, while nutrient intake and diet quality were assessed using the Nutrient-Rich Food 9.3 Index Score (NRF 9.3). Subsequently, the collected data underwent both univariate and multivariate analyses. Potential biases might arise due to time constraints during the pandemic and reliance on self-reported online data. Moreover, the method used to measure nutrient intake might not be ideal for this demographic, lacking tailored tests. Nonetheless, it's important to highlight that the survey underwent prior validation among Indonesian adults, affirming its broad applicability.

**Results:** Female users showed low average NRF 9.3 scores (241.67), indicating poor diet quality. Their prioritized food choice motives were also low. Significant associations surfaced between NRF 9.3 scores and food choice motives—tradition ( $p < 0.01$ ,  $r: 0.229$ ), comfort ( $p < 0.01$ ,  $r: 0.223$ ), organic ( $p < 0.01$ ,  $r: 0.231$ ), safety ( $p < 0.001$ ,  $r: 0.162$ ), weight control/health ( $p < 0.01$ ,  $r: 0.171$ ), and income ( $p < 0.05$ ).

**Conclusion:** The NRF 9.3 score is likely to increase when there are higher scores for tradition, comfort, and organic factors, and when income exceeds the minimum regional wage.

**Keywords:** diet quality, food choice motives, NRF 9.3, female online food delivery users

### Introduction

Extensive literature has documented the profound impact of dietary quality on health and well-being. It is widely acknowledged that low dietary quality significantly contributes to health issues due to deficiencies in essential nutrients. For instance, inadequate iron intake leading to iron-deficiency anemia<sup>1</sup>, and diets rich in unhealthy

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components such as calories, saturated fats, trans fats, and sugars, have been linked to weight-related problems, notably obesity.<sup>2</sup> Moreover, the association between poor dietary quality and a spectrum of health conditions, including heart disease, diabetes, cancers, and musculoskeletal disorders,<sup>3</sup> has been thoroughly explored.

While numerous studies have addressed the implications of poor dietary habits, recent literature has taken a novel direction by examining the shifts in dietary behaviors during the COVID-19 pandemic. Studies published in sources like Obesity Reviews and research conducted in Indonesia highlight altered eating habits during the pandemic, indicating a decline in diet quality, particularly among women.<sup>4</sup> This emerging trend underscores a critical gap in understanding how crises like the pandemic influence dietary choices and quality.

Furthermore, the surge in reliance on online food delivery services during the pandemic has emerged as a significant aspect of dietary behavior. This shift raises intriguing questions about the interplay between food choice motives and diet quality during such crises—a facet that remains relatively unexplored in current literature.<sup>5</sup>

While existing studies have proposed various indices and methodologies to evaluate diet quality, such as the Nutrient-Rich Food (NRF) Index, their application and assessment amid the unique circumstances of the COVID-19 pandemic have received limited attention. Therefore, this study aims to bridge this gap by exploring the Nutrient-Rich Food Index 9.3 score and its correlation with food choice motives, particularly among female users of online food delivery services. This research aims to offer a new perspective on the evolving landscape of dietary behavior during an emergent context, contributing new knowledge by quantitatively associating the Nutrient-Rich Food Index 9.3 Score with food choice values within this demographic.

## Methods

This cross-sectional online survey, conducted in Indonesia, utilized the *Limesurvey*<sup>®</sup> web-based application. Employing consecutive convenience sampling, 405 female online food delivery users from the *Jabodetabek* (Jakarta, Bogor, Depok, Tangerang, and Bekasi) area were selected based on specific inclusion and exclusion criteria. The study focused on assessing the association between the Nutrient-Rich Food 9.3 (NRF 9.3) index score and singularly evaluated food choice values.

Data collection commenced in February and March 2023 after obtaining ethical clearance from the Faculty of Medicine at Universitas Indonesia (approval number KET-85/UN2/F1/ETIK/PPM.00.02/2023) and involved questionnaires covering screening queries, sociodemographic details, and the Food Choice Values Questionnaire. The Nutrient-Rich Food 9.3 scores were derived from the SQ-FFQ, capturing dietary intake. Analytical processes, encompassing univariate to multivariate analysis, were performed using SPSS 20.

However, it is imperative to note potential biases introduced due to reliance on self-reported measurements, particularly concerning the SQ-FFQ's methodology. Despite prior validation among Indonesian adults, limitations persisted as the food list might not entirely represent female online food delivery users. Moreover, this study faced constraints in data comprehensiveness, limiting insights into energy intake underestimation, owing to restricted available data, comprising solely age and gender information.

## Results

The sociodemographic characteristics of the subjects are presented in **Table 1** below. 65.9% of the total subjects were aged between 19 and 29 years old. The majority of them are private employees (27.4%) and college students (24.9%). Those who have an occupation have an income above MRW (49.6%). Most of them are not married (59%) and they have a nuclear family

(86.2%) with less than equal to 4 members left at home (67.7%). The two most popular online food delivery apps that they usually use are *GoFood* (50.6%) and *GrabFood* (36%). Other apps, such

as *ShopeeFood* (11.9%), are also likely to be used for ordering food online.

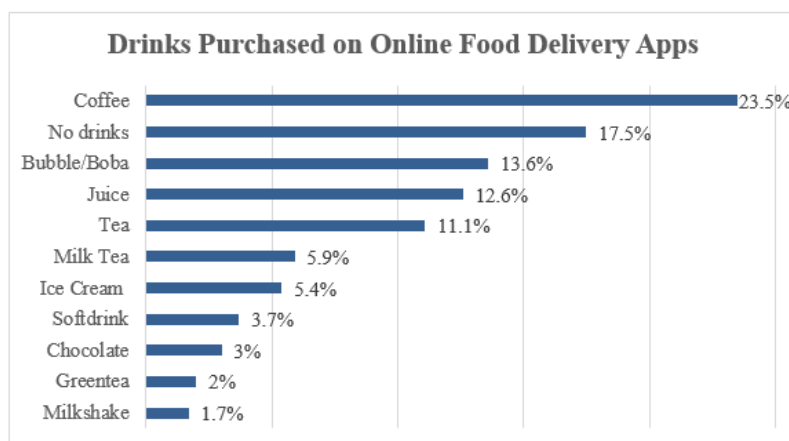
**Figures 1** and **2** show the kinds of food and beverages they purchased on an online food delivery app in the last 7 days.

**Table 1.** Sociodemographic characteristics of the subjects (n=405)

Characteristics	n	%
<b>Age (years)</b>		
19 – 29 years old	267	65.9
30 – 49 years old	110	27.2
50 – 64 years old	28	6.9
<b>Occupation</b>		
Unemployed	6	1.5
College Student	101	24.9
Housewife	49	12.1
Private Employee	111	27.4
Civil Servant	48	11.9
Contract Worker	35	8.6
TNI/Police	-	-
Entrepreneur	48	11.9
Retired	7	1.7
<b>Income</b>		
Above MRW	201	49.6
Under or equal to MRW	85	21
No Income	119	29.4
<b>Marital Status</b>		
Married	166	41
Not Married	239	59
<b>Family Type</b>		
Nuclear Family	349	86.2
Extended Family	56	13.8
<b>Family Size</b>		
> 4	131	32.3
≤ 4	274	67.7
<b>Online Food Delivery Apps</b>		
GoFood	205	50.6
GrabFood	146	36
Fast Food Delivery Apps	6	1.5
Others	48	11.9



**Figure 1.** Food purchased in the last 7 days



**Figure 2.** Beverages purchased in the last 7 days

The results found that the most commonly purchased foods are chicken dishes (*ayam geprek*) (23.2%) and fast food (14.3%). For beverages, they commonly purchased coffee (23.5%) and bubble drinks or boba (13.6%).

Based on the prior study, the FCVQ exhibited values ranging from 0.4 to 0.9, signifying the strong validity of its items. Additionally, Cronbach's alpha, used to assess the questionnaire's reliability, yielded a value of 0.889 for the FCVQ.<sup>6</sup> **Table 2** presents the median scores attributed to food choice motives. Sensory appeal and organics emerged as the most significant factors influencing decisions regarding food selection and consumption, each receiving a median score of 14. Following closely, access and convenience garnered median scores of 13 and 12, respectively. Among respondents, tradition was identified as the least influential factor.

**Table 2.** Food choice motives of the subjects (n=405)

Food Choice Motives	Median (Q1-Q3)
Convenience	12 (10 – 14)
Access	13 (12 – 15)
Tradition	8 (6 – 9)
Safety	11 (10 – 12)
Organic	14 (12 – 15)
Comfort	11 (9 – 13)
Sensory Appeal	14 (12 – 15)
Weight Control/Health	9 (8 – 11)

The NRF 9.3, validated for assessing nutrient density, encompasses nine recommended nutrients while restricting three others. It computes the nutrient density score by subtracting the percentage daily reference values (DRVs) of limited nutrients from the recommended ones, aiming for a diet quality closer to the maximum score of 900. Using a Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ), participants reported food consumption frequencies and portion sizes. Nutrient intake was computed from *Tabel Komposisi Pangan Indonesia* (TKPI)<sup>7</sup>, United States Department of Agriculture (USDA)<sup>8</sup>, and *Survey Konsumsi Makanan Individu* (SKMI)<sup>9</sup> datasets in Microsoft Excel. Nutrient-Rich (NR) and Limiting Nutrient (LIM) foods were pinpointed via Nutrient-Rich Food algorithm calculations, comparing intake against recommended and maximum daily values. The Nutrient-Rich Food Index 9.3 score was derived from the disparity between NR and LIM values. Based on **Table 3**, it was observed that the nutrient intake among the Female Online Food Delivery users was generally low, with most nutrients falling below the recommended RDA levels, except for vitamin D, which was relatively sufficient at 115%. This indicates that the participants' diets were lacking in essential nutrients, raising concerns about potential nutrient deficiencies and their impact on overall health.

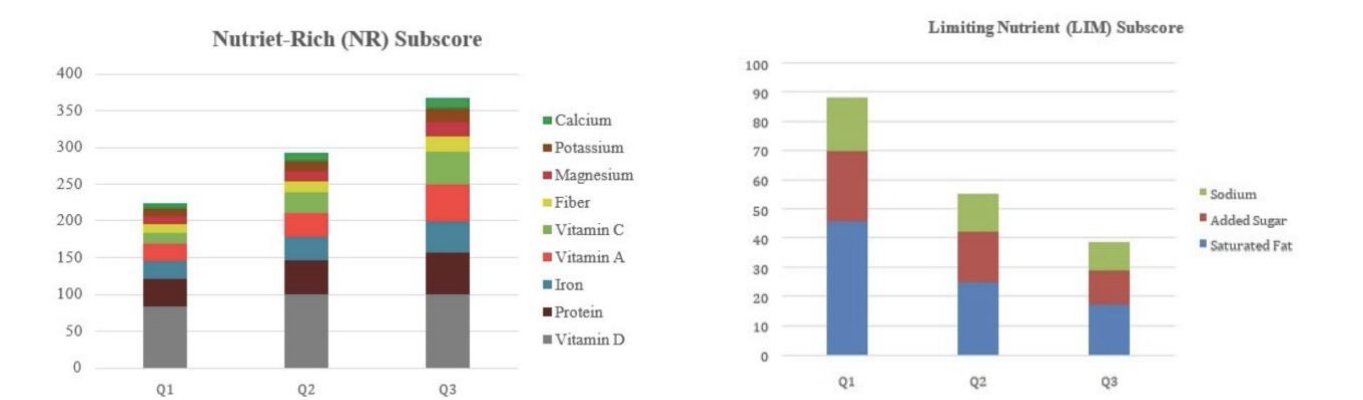
This study also revealed that the average NRF 9.3 score among female online food delivery users

was 241.67, which is considered very low when compared to the maximum possible NRF score of 900. **Figure 3** provides an overview of how the NRF 9.3 was constructed, and it was used in this study to assess diet quality. The figure demonstrates that the percent daily values for index nutrients increased with higher quartiles of

the NRF 9.3 score, while the LIM subscore, on the contrary, decreased. As expected, transitioning from the lowest (Q1) to the highest quartiles (Q3) of NRF 9.3 scores was associated with an increase in the percent daily values of nutrients to encourage and a corresponding decrease in the percent daily values of nutrients to limit.

**Table 3.** Nutrient intake and percentage based on RDA among female online food delivery users during COVID-19 pandemic (n=405)

Nutrient	Median (Q1-Q3)	% RDA <sup>a</sup>
Protein (grams)	27.11 (21.77 – 34.03)	45% (36% - 57%)
Fiber (grams)	4.72 (3.32 – 5.99)	15% (11% - 20%)
Vitamin A	200.69 (138.45 – 309.30)	33% (23% - 52%)
Vitamin C	20.34 (12 – 33.77)	27% (16% - 45%)
Vitamin D	17.25 (12.49 – 21.59)	115% (83% - 144%)
Iron	4.76 (3.71 – 6.08)	26% (21% - 34%)
Calcium	112.30 (79.1 - 142)	11% (8% - 14%)
Potassium	641.27 (478.54 – 882.41)	14% (10% - 19%)
Magnesium	47.87 (34.65 – 66.28)	14% (10% - 20%)
Saturated Fat	4.95 (3.39 – 9.11)	25% (17% - 46%)
Sodium	320.91 (226.25 – 437.49)	13% (9% - 18%)
Added Sugar	8.51 (5.86 – 11.98)	17% (12% - 24%)



**Figure 3.** Nutrient subscore of the Nutrient-Rich Food 9.3 Index (NRF 9.3) by quartiles (Q1, Q2, Q3) of total NRF 9.3 scores

Given the non-normal distribution of the data, Spearman correlation and non-parametric tests were employed. Spearman correlation was utilized to evaluate the relationship between the NRF 9.3 score and food choice motives. As shown in **Table 4**, a significant positive correlation was observed between the NRF 9.3 score and tradition, comfort, organic, safety, and weight control/health. These correlations were

statistically significant, although their strengths varied. Notably, the correlations between the NRF 9.3 score and safety ( $r = 0.162$ ) and between weight control/health ( $r = 0.171$ ) were very weak. Conversely, the correlations between the NRF 9.3 score and tradition ( $r = 0.229$ ), comfort ( $r = 0.223$ ), and organic ( $r = 0.231$ ) were weak. These findings indicate differing prioritization among female online food delivery users concerning

tradition, comfort, organics, safety, and weight control/health in relation to nutrient-rich food scores.

**Table 4.** Correlation between NRF 9.3 index score and food choice values (n=405)

Food Choice Values	NRF 9.3	
	<i>r</i>	<i>p</i>
Convenience	0.064	0.201
Access	-0.005	0.916
Tradition	0.229	< 0.01**
Comfort	0.223	< 0.01**
Organic	0.231	< 0.01**
Safety	0.162	0.001**
Sensory Appeal	0.003	0.956
Weight Control/Health	0.171	< 0.01**

Statistical analysis used Spearman correlation test

\*Significance level at P-value < 0.05; \*\*Significance level at P-value < 0.01

In **Table 5**, the association between the NRF 9.3 score and sociodemographic characteristics is examined. The results indicate that there is no significant difference in the NRF 9.3 score among the age groups of 19-29, 30-49, and 50-64 years (p-value > 0.05). Furthermore, there is no significant difference (p-value > 0.05) in the associations between the NRF 9.3 score and occupation, marital status, family type, family size, and online food delivery app. In contrast, the results demonstrate a significant difference (p-value < 0.05) in the association between income and the average NRF

9.3 score among female online food delivery users during the COVID-19 pandemic. Females with an income higher than the minimum regional wage (MRW) exhibited the highest average NRF 9.3 score of 251.82, indicating a healthier diet compared to those with no income (235.03) and those with income equal to or below the MRW (226.92).

As shown in **Table 6**, the variables included in the analysis, which consisted of convenience, tradition, comfort, organic, safety, weight control/health, income, and marital status. The inclusion criteria for these variables were based on a p-value < 0.2 in the bivariate analysis. Based on the final model, the tradition score, comfort score, organic score, and income emerged as significant predictors of the Nutrient-Rich Food

Index 9.3 Score among female users of online food delivery during the COVID-19 pandemic, after adjusting for other variables.

### Discussion

The study found that over half of female online food delivery users were 19–29 years old. This age group has good digital literacy, making them eager to socialize, study, and create digital content.<sup>10</sup> This aligns with Gomes et al.'s 2022 findings, which showed that younger customers are more likely to purchase food online during a pandemic due to their enhanced technological skills, desire for innovative consumption, and perception of the positive aspects of online shopping, such as time savings, convenience, price comparison, and access to a variety of products.<sup>11</sup> The majority of female users in this study are private employees and college students. Candra S. et al. found that the majority of female users in this study are private employees and college students who primarily work as workers.<sup>12</sup> Kartono et al. found that these individuals may be less flexible due to their commitments and time limitations, requiring practical services to provide food and beverages.<sup>10</sup>

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**Table 5.** NRF 9.3 associated with socio-demographic characteristic (n=405)

Variables	NRF 9.3		p value
	Mean	Median (min-max)	
<b>Age</b>			
19 – 29 years old (n=267)	240.26	221.96 (69.21 – 550.35)	0.302 <sup>a</sup>
30 – 49 years old (n=110)	246.57	230.71 (90.22 – 467.31)	
50 – 64 years old (n=28)	235.69	200.69 (148.84 – 455.22)	
<b>Occupation</b>			
Unemployed (n=6)	250.69	258.03 (188.05 – 298.71)	0.681 <sup>a</sup>
College Student (n=101)	232.81	219.87 (113.93 – 481.64)	
Housewife (n=49)	262.61	229.92 (135.39 – 467.31)	
Private Employee (n=111)	244.69	220.80 (69.21 – 550.35)	
Civil Servant (n=48)	240.46	223.13 (119.03 – 431.54)	
Contract Worker (n=35)	224.70	212.83 (90.22 – 416.57)	
Entrepreneur (n=48)	242.00	223.26 (143.70 – 480.87)	
Retired (n=7)	257.66	256.29 (153.37 – 435.26)	
<b>Income</b>			
Above MRW (n=201)	251.82	229.50 (90.22 – 550.35)	0.014 <sup>a *</sup>
Under or equal to MRW (n=85)	226.92	206.97 (69.21 – 491.22)	
No Income (n=119)	235.03	219.87 (113.93 – 455.22)	
<b>Marital Status</b>			
Married (n=166)	250.51	226.42 (103.28 – 480.87)	0.200 <sup>b</sup>
Not Married (n=239)	235.52	221.96 (69.21 – 550.35)	
<b>Family Type</b>			
Nuclear Family (n=349)	241.73	223.46 (90.22 – 550.35)	0.956 <sup>b</sup>
Extended Family (n=56)	241.22	219.39 (69.21 – 455.22)	
<b>Family Size</b>			
> 4 (n=131)	245.77	226.38 (69.21 – 481.64)	0.464 <sup>b</sup>
≤ 4 (n=274)	239.70	221.56 (90.22 – 550.35)	
<b>Online Food Delivery (OFD) App</b>			
<i>GoFood</i> (n=205)	243.00	219.87 (113.93 – 550.35)	0.879 <sup>a</sup>
<i>GrabFood</i> (n=146)	241.45	224.29 (90.22 – 491.22)	
Fast Food Delivery App (n=6)	241.05	218.57 (69.21 – 455.22)	
Others (n=48)	236.68	228.18 (126.32 – 374.51)	

<sup>a</sup>Statistical analysis used Kruskal Wallis; <sup>b</sup>Statistical analysis used Mann-Whitney U

NRF9.3: Nutrient-Rich Food 9.3

\*Significance level at p-value &lt;0.05

**Table 6.** Multiple linear regression analysis of NRF 9.3 (n=405)

Parameter	<sup>a</sup> NRF 9.3			
	Parameter Estimate	Standard Error	95% CI	p-value
Constant	114.023	27.805	80.604 – 263.641	
Convenience	-2.049	1.754	-8.109 – 1.547	0.243
Tradition	5.628	2.025	4.409 – 15.564	0.006*
Comfort	6.237	1.447	4.649 – 12.611	<0.001**
Organic	4.707	2.271	-0.749 – 11.763	0.039*
Safety	0.597	2.513	-5.272 – 8.551	0.812
Weight Control/Health	0.671	2.095	-4.155 – 7.408	0.749
Income	-9.390	4.348	-25.922 – (-2.004)	0.031*
Marital Status	-11.191	8.065	-57.391 – (-3.201)	0.166

<sup>a</sup>Dependent variable: NRF9.3

The multiple linear regression equation is given by: NRF9.3 (score) = 114.023 + 5.628 (tradition) + 6.237 (comfort) + 4.707 (organic) – 9.390 (income), depending on tradition score, comfort score, organic score, income (1 = above MRW, 2 = under or equal to MRW, 3 = no income), of the subjects

\*Significance level at P-value <0.05; \*\*Significance level at P-value <0.01

R square = 17%, P-value = <0.01 analyzed with multiple linear regression using enter method

Almost half of the employed female users have a higher income than Rp4.641.854. Data from Statista 2021 shows high incomes holding the largest share (45.26%).<sup>13</sup> This aligns with a 2022 study by Gomes S. et al., which found that consumers with higher incomes were more likely to purchase online during the pandemic.<sup>11</sup> These individuals are busier at work and have more flexibility in spending, making them more likely to prefer online purchases. Over half of the subjects are not married and have a nuclear family with less than four members. A 2022 study by Algheshairy et al. found that food delivery apps were easy for unmarried women, but their duty towards meal planning and home-meal preparation appeared deficient.<sup>14</sup> Over half of female users used GoFood for online food delivery, similar to a 2020 study by Iisnawati et al. where 43% of females used the app.<sup>15</sup> Kartono et al. found that most online food users prefer heavy foods over snacks and beverages to satisfy cravings.<sup>10</sup> The study surveyed participants about their recent food and beverage purchases in the last 7 days. The most frequently purchased foods were chicken dishes, hamburgers, pizza, spaghetti, and fast food. Female users frequently purchase coffee and boba drinks as beverages, while some do not consume them. The 2021 study

by Martha E. et al. found that fast food, chicken dishes, bubble tea, coffee, and sweet cakes were the most popular food and drink orders.<sup>16</sup>

The results of the study revealed that sensory appeal and organic factors had the highest median scores among the food choice motives. Sensory appeal plays a significant role in consumers' perception, purchase decisions, consumption, and satisfaction with convenience foods.<sup>17,18,19</sup> When female online food delivery users browse through the food options available on online delivery apps, the visual appearance of the food becomes the initial criterion for determining its appeal, even before they have a taste. Previous research by Samson L. et al. in 2019 demonstrated that sensory appeal can capture attention, evoke emotions, and influence individuals' preferences for healthy foods that are being promoted.<sup>20</sup> Moreover, according to Prabowo and Nugroho, individuals with prior experience in online food delivery tend to make purchasing decisions based on their previous online shopping experiences.<sup>21</sup> These experiences influence their intentions to repurchase certain products, including food.

Based on Nunes F. et al.'s study in 2021, the most important factor influencing the purchase of organic food is the perceived health benefits.<sup>22</sup> Other organic concerns include the use of natural

ingredients, vitamin and mineral content, and environmental considerations. In a recent study by Zhen Rong et al. in 2021, it was found that the participants expressed a strong interest in ordering healthy food through online food delivery apps in the future.<sup>23</sup> Additionally, a majority of participants agreed that providing more nutritional information could encourage them to choose healthier meal options when using online food delivery apps. Therefore, it can be inferred that female online food delivery users prioritize organic food when making purchasing decisions for the sake of their health. This inference is supported by the study's results, particularly among females aged 30-49 years and 50-64 years. This finding aligns with a study conducted in China, which indicated that adults over the age of 40 placed greater importance on organic food compared to younger age groups.<sup>24</sup>

According to a study conducted by Brata *et al.*, in 2022 on consumers' perceptions of organic food products during the COVID-19 pandemic, there was an increased awareness among people about the products they purchase.<sup>25</sup> This led to an increased consumption of organic food due to its perceived higher quality, nutritional value, and environmental friendliness compared to other food products. The findings of the current study support previous research in this area, which identified key factors that influence consumers' decisions to buy organic products. These factors include intrinsic qualities of the product, such as superior quality, freshness, and perceived health benefits. However, based on the data collected in this study, it was observed that the majority of female users of online food delivery in the past 7 days did not prioritize organic food. This might be attributed to the fact that the majority of participants in this study were females under the age of 30, and their main focus was on satisfying their immediate preferences rather than prioritizing organic choices. This finding aligns with another study by Martha E. *et al.*, which highlighted the importance of satisfaction, social environment, and food preferences in online food delivery.<sup>16</sup>

Access was identified as the second-highest factor influencing the food choices of female

users. The concept of access includes considerations such as price, distance, and ease of finding the desired food. In this study, female users of online food delivery expressed the importance of food being easily accessible and providing value for the money spent. This aligns with a previous study by Yeo *et.al* which found that online food delivery platforms often offer promotions and discounts to customers.<sup>26</sup> Additionally, online food delivery services can reach customers in different geographic locations, as they partner with a wide range of restaurants. By using online food delivery apps, customers can overcome obstacles such as transportation costs and save time by avoiding physical visits to restaurants. While there may be a delivery fee associated with online food delivery, it is viewed as a convenient alternative by customers.

Convenience refers to the time saved or the ease of purchasing and preparing food. A study by Soric et al. in 2021 highlighted the increased importance of convenience, particularly among women, during the pandemic. It was found that women tend to place a higher value on convenience in their food choices.<sup>27</sup> Additionally, according to Chowdhury R. et al. in 2022, customers often prefer online shopping due to the convenience of shopping from home and having more free time. This shift has led to the growing popularity of online food delivery services, especially among urban consumers and the working population.<sup>28</sup>

The factor that subjects consider the least when deciding which foods to purchase is tradition. This finding is consistent with the study by Rahmasari et al., which reported that tradition had the lowest median score. Traditions reflect an interest in the familiarity, cultural, and traditional aspects of food.<sup>29</sup> In this study, tradition received a median score of 8, particularly among the older age group. Similarly, the previous study observed that concerns about tradition increased significantly with age, indicating that older respondents place higher importance on tradition.

The study reveals that most female online food delivery users exhibit low intake of essential nutrients, such as protein, fiber, vitamins A and C, iron, calcium, potassium, and magnesium—

except for vitamin D. This deficit may stem from underestimating energy intake, affecting overall nutrient consumption. Barbara E et al.'s study notes that energy intake serves as a foundation for dietary assessment, impacting other nutrient estimations.<sup>30</sup> When total energy intake is underestimated, it extends to undervaluing associated macronutrients, minerals, and vitamins. Calculating energy intake underestimation typically involves contrasting reported energy intake (EI) with estimated energy requirements (EER) or total energy expenditure (TEE). Common methods, like the Harris-Benedict equation and the Goldberg cutoff method, assess this discrepancy.<sup>31</sup> However, due to limited data—only age and gender—the latter method couldn't be employed in this study.

Another probable reason for inadequate nutrient intake among female users might be the SQ-FFQ's food list misalignment with their dietary habits. Insufficient representation of essential nutrients in the questionnaire's food choices could lead to suboptimal intake among participants. Protein intake among users satisfies only 45% of the Recommended Dietary Allowance (RDA), remaining insufficient.<sup>32</sup> The protein intake observed in this study remains low when contrasted with another study conducted in 2022, where adult women reported a protein intake of 51.1%.<sup>33</sup> Similarly, inadequate fiber and iron intake were observed, impacting overall diet quality and variety.<sup>34</sup> These deficiencies align with national data on vitamin A, C, and calcium insufficiency<sup>35</sup>, signifying significant health concerns.<sup>36</sup>

Insufficient potassium and magnesium intake among female users hold significance for metabolic syndrome, affecting cardiovascular health and glucose metabolism. Low levels of these minerals have been linked to high blood pressure, insulin resistance, and increased risks of developing metabolic syndrome and type 2 diabetes. Despite a wide array of food choices offered by online delivery services, the average NRF 9.3 score among female users remains notably low at 241.67 out of 900, indicating suboptimal nutrient-rich diets.

The prevalence of nutrient-poor diets, particularly high-fat, sugary, and salty foods among Indonesian adults<sup>37</sup>, may influence choices made through online delivery platforms. These shifts in dietary behaviors, especially during the pandemic, signify a preference for less nutrient-dense options.<sup>38</sup> The findings suggest a need for a greater focus on promoting healthier food choices within these delivery platforms to improve the nutritional well-being of users.

According to this study, sensory appeal, access, and convenience did not significantly correlate with the NRF 9.3 score. Sensory appeal, while influencing preferences, doesn't guarantee nutritional quality, leading to the consumption of foods high in unhealthy elements during the pandemic. Access to diverse foods doesn't assure healthy choices, affected by factors like food deserts. Convenience influences food choices<sup>39</sup>, yet convenience foods often lack nutrients, contributing to poor diet quality.<sup>40</sup>

Examining food choice motives revealed varying priorities linked to a lower NRF 9.3 score, indicating increased reliance on processed foods, deviating from traditional diets. Younger generations tend to prioritize global food trends over traditional nutrient-rich foods. Tradition, comfort, organic choices, and health concerns influence food choices but don't consistently align with optimal nutrition.<sup>41</sup> Comfort foods offer emotional satisfaction<sup>42</sup> but often contain unhealthy elements, seen in food choices of online delivery users. Health-related concerns like organic choices, food safety, and weight control didn't reflect in the NRF 9.3 score. Ensuring food safety and considering health goals are pivotal in making conscious food choices.

This study examined how sociodemographic factors relate to NRF 9.3. Out of various factors like age, occupation, family size, family type, marital status, and use of online food delivery, only income showed a significant difference in NRF 9.3 scores. Notably, females with higher incomes above MRW displayed the highest NRF 9.3 average score at 251.82, indicating a healthier diet compared to those with no income (235.03) or incomes equal to or below MRW (226.92). Supporting research by Gómez G et al. in 2021

found that individuals with lower socioeconomic status tend to consume fewer fruits, vegetables, whole grains, fiber, and fish compared to those with higher status.<sup>43</sup> Higher income levels typically afford greater access to nutrient-rich foods like fresh produce, lean proteins, and whole grains, which can be relatively more expensive than processed options. Studies, including Rehm, C. D., Monsivais, P., and Drewnowski, A, also confirm that higher-income individuals tend to have better overall diet quality and consume more nutrient-rich foods.<sup>44</sup>

The multivariate analysis in this study revealed a significant trend among female online food delivery users. Those who placed less emphasis on tradition, comfort, and organic choices while having an income above the minimum regional wage showed remarkably lower NRF9.3 scores. This aligns with prior research indicating a decline in diet quality during the pandemic, attributed partially to shifting food preferences.<sup>45</sup>

Tradition, comfort, and organic preferences are linked to health considerations in food choices. Although not directly tied to physical health, these factors shape dietary patterns, influencing overall well-being. Organic choices, often associated with reduced pesticide exposure and potential nutrient richness, hold relevance in health-related decisions.<sup>46</sup> Neglecting health-related factors can contribute to poor diet quality, shifting choices toward taste, convenience, or cultural norms. This can result in diets high in unhealthy components while lacking essential nutrients, elevating the risk of chronic diseases.<sup>47</sup>

However, the variables explored in our regression model collectively explain only 17% of the impact on NRF 9.3. Further investigations are necessary to better understand how other health and nutrition-related factors intertwine with NRF 9.3.

## Conclusion

Among female online food delivery users, the majority (65.9%) were aged between 19 and 29, employed in the private sector (27.4%), and earned incomes above the minimum regional wage (49.6%). Notably, over half were unmarried

(59%) and resided in nuclear families (86.2%) with fewer than four household members (67.7%), with GoFood being the preferred delivery app (36%). While these users favored sensory appeal and organics in food choices, tradition held limited significance. However, their average NRF 9.3 score was notably low, averaging 241.67 out of 900, indicating insufficient intake of vital nutrients such as protein, fiber, vitamins A and C, iron, calcium, potassium, and magnesium. Factors such as tradition, comfort, organics, safety, and income displayed positive correlations with the NRF 9.3 score, influencing users' dietary decisions. Lower emphasis on these factors and incomes below the regional wage were associated with reduced NRF 9.3 scores, persisting even after adjusting for other variables. Greater emphasis on tradition, comfort, and organics, coupled with higher incomes, corresponded to higher NRF 9.3 scores.

Different recipes and culinary traditions greatly impact the nutritional makeup of dishes. Across regions, variations in ingredients, oils, and cooking styles significantly affect the nutrient profiles. For instance, one recipe might focus on vegetables or lean proteins, while another could emphasize certain spices or fats. Culinary traditions, like the Mediterranean diet's emphasis on olive oil and fresh produce, offer high levels of healthy fats and antioxidants. Similarly, Asian cuisines featuring seafood, tofu, and distinctive spices present diverse nutrient compositions. Even within a single cuisine, variations in ingredients used by different restaurants can affect fat content. Nutrient levels also vary based on seasonal availability, with dishes using fresh seasonal produce differing from those relying on frozen or out-of-season ingredients. Cooking methods like grilling, frying, or baking influence fat content, while portion sizes are crucial in determining overall calorie intake.

## Conflict of interest

Authors declared no conflict of interest regarding this article.



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## Analysis of macronutrient and micronutrient intake with the incidence of stunting and wasting in toddlers 0-59 months of age at public health center in Bojong, Bogor regency, Indonesia

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### Abstract

**Background:** Stunting is defined as not achieving optimal height for age. One of the factors of stunting is caused by unbalanced nutrition. This is due to long-term nutrient intake inadequacies that potentially lead to insufficient nutrient requirements from food. Wasting often has symptoms of severe weight loss in the short term. It usually occurs when toddlers do not get a good quality and quantity of food and/or they suffer from recurrent or chronic illnesses.

**Objective:** Assessing the relationship between macro-micronutrient intake with the incidence of stunting and wasting in the Bojong Health Center working area, Bogor Regency July-August 2023 Period.

**Methods:** This research using cross-sectional study was conducted in the working area of Public Health Centre Bojong, Bogor Regency, Indonesia, from July 2023 to August 2023. The number of subjects is 93 subjects. Subjects were recruited using consecutive sampling, toddlers aged 0-59 months and mothers were the respondents who answered questions during interviews, 2x24-hour food recall, SQFFQ. The data in this study was obtained through direct interviews with respondents.

**Results:** Subject macronutrient and micronutrient intake tended to be deficient refer to RDA 2019. There was an association ( $p=0.000$ ) between the intake of energy, protein, carbohydrates, fat, Fe, Omega 3, Zn, vitamin D, and Ca with the incidence of stunting and wasting.

**Conclusions:** Intakes of energy, protein, carbohydrate, fat, iron, omega-3, zinc, vitamin D, and Ca were significantly lower in children with nutritional problems (stunting and wasting) compared to RDA Indonesian Ministry of Health 2019.

**Keywords:** stunting, wasting, macronutrient, micronutrient, toddlers 0-59 months

### Introduction

Every child has the right to receive food and nutrients to improve brain growth and intelligence. Nutrient intake is a necessity that plays an important role in growth, especially brain development. Children's growth and development

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depends on a balanced intake of nutrients. Intake of nutritious food is an important requirement for development, especially the development of children's cognitive. One's ability to development depends on a balanced intake of nutrients.<sup>1</sup>

Stunting is defined as not achieving optimal height for age. The causes of stunting are chronic or recurrent undernutrition, commonly associated with poverty, poor maternal health and nutrition, a history of illness and/or inappropriate feeding and care in early life.<sup>2</sup> One of the factors of stunting in children is caused by unbalanced nutrition. This is due to long-term nutrient intake inadequacies that potentially lead to insufficient nutrient requirements from food. Stunting occurs when the baby is still in the womb but does not appear until the child is 2 years old. Growth retardation can have profound effects on the health status of the child.<sup>3</sup>

Wasting is defined as low body weight compared to height. Wasting often has symptoms of severe weight loss in the short term. It usually occurs when toddlers do not get a good quality and quantity of food and/or they suffer from recurrent or chronic illnesses.<sup>4</sup> Several previous studies have also shown a relationship between intake and the incidence of malnutrition, especially stunting and wasting.<sup>5-8</sup>

Based on Basic Health Research (RISKESDAS) data in 2018, it is known that the prevalence of stunting aged 0-59 months in Indonesia in 2018 was 30.8%, consisting of a prevalence of shortness of 19.3% and very short of 11.5%. The prevalence of undernutrition and malnutrition aged 0-59 months according to the 2018 Riskesdas was 10.2%. This shows that Indonesia is experiencing severe public health challenges in the case of stunting and wasting toddlers. Bogor Regency is one of the regions in West Java Province with a stunting prevalence of 28.6% and a wasting prevalence of 4.2%. This makes it one of the top 7 regions in West Java with the highest prevalence of stunting.<sup>9</sup> Although the prevalence of wasting in Indonesia and West Java is below the threshold, it needs to be a concern to prevent future spikes.

The intake of these macronutrients is a major contributor to energy, which is the main source of

muscle growth.<sup>10</sup> While micronutrients are used in small amounts, but have a very vital role in the formation of hormones, and enzyme activity, and regulate the function of the reproductive system.<sup>11</sup> Determinants that cause macro and micronutrient problems are lack of parental knowledge related to nutrition and economic factors that can affect the selection of food types and food diversity.<sup>12</sup> Therefore, the study aimed to determine the relationship between macro and micronutrient intake and the incidence of stunting and wasting in toddler 0-59 month at the Bojong Health Center working area, Bogor Regency, West Java, Indonesia.

## Methods

### *Study population and design*

A cross-sectional study was conducted in the working area of Public Health Centre Bojong, Bogor Regency, Indonesia, from July 2023 to August 2023 without using a pretest. The number of subjects used the Lemeshow formula and obtained 93 subjects. Subjects were recruited using consecutive sampling, with inclusion criteria of toddlers aged 0-59 months, were patients of the nutrition clinic of Bojong Health Centre, resided in the working area of Bojong Health Centre, Bogor Regency, and were willing to become research subjects by signing the informed consent form. The exclusion criteria for this research subject were subjects who were sick during data collection. Subjects were toddlers aged 0-59 months and mothers were the respondents who answered questions during interviews. The main result of this study is the correlation between macronutrient and micronutrient intake with the incidence of stunting and wasting of toddlers aged 0-59 years in the Bojong Health Centre working area.

### *Data collection*

Data collection was carried out using primary data. The data in this study was obtained through direct interviews with respondents including respondent characteristics, 2x24-hour food recall,

SQFFQ and direct subject measurements to determine the nutritional status of subjects by measuring the child's height and weight using a microtoise measuring instrument and a child's weight scale.

Interviews were conducted by clinical nutrition specialists, nutritionists, and several enumerators who had been trained for one month to fill out questionnaires, 2x24-hour food recall forms and SQ FFQ. The 2x24 hour food recall interview was assisted using the Porsimetry Book Kemenkes RI to visualize the food intake and gave aid in the food portion size estimation. Meanwhile, the SQ FFQ form uses the general one. All forms used are forms that have been validated and used in previous research.

*Data analysis*

Data was input and analyzed using Windows's SPSS version 26. Normal data distribution was assessed if the p-value was >0.05 using the Kolmogorov-Smirnov test. The mean and standard deviation are used to describe normally distributed data, and conversely the median is used with minimum-maximum values. The Pearson or Spearman correlation test was used to analyze the correlation between variables, with a p-value <0.05 considered significant. Linear regression test is used to confirm variables.

Food intake from the 2x24 hour food recall is input into the Nutrisurvey application using the Indonesian Food Composition Table database. The SQFFQ form is used to determine the subject's dietary habits.

*Ethical approval*

This research has been approved by the Health Research Ethics Committee of UPN Veteran Jakarta (UPNVJ) with Ethics Approval number 352/VIII/2023/KEPK.

**Results**

Data on subject characteristics was obtained using direct interviews with respondents and direct

measurements of the subject's weight and height carried out by a nutritionist.

Based on **Table 1**, the results of toddlers 0-59 months were 38 people (40.9%) were male and 55 people (59.1%) were female. According to the height for age z-score calculation, 67 people (72%) of respondents experienced severe stunting, 14 people (15.1%) experienced stunting and 12 people (12.9%) were normal. In the calculation of the weight for height z-score, the results of respondents who experienced stunting were 60 people (64.5%), 28 people (30.1%) were normoweight and as many as 5 people (5.4%) were overweight.

Based on **Table 2**, the intake of macronutrients energy (24.7%), protein (15.1%), carbohydrates (24.7%), and fat (19.4%) tended to be deficient.

In addition, the intake of micronutrients Fe (22.6%), Omega 3 (23.7%), Zn (22.6%), Vitamin D (22.6%), and Ca (17.2%) showed that the average intake of respondents tended to be deficient.

**Table 3** shows the results of the analysis of the relationship between nutrient intake and the incidence of stunting in toddlers, it was found that less energy intake mostly affected the incidence

**Table 1.** Subject's characteristics (n=93)

Category	n	%
Sex		
Male	38	40.9
Female	55	59.1
BW/A		
Severe Stunting <-3SD Z Score	67	72
Stunting <-2 SD Z Score	14	15.1
Normal -2 SD ≤ 2SD Z Score	12	12.9
BW/BH		
Wasting <-2 SD Z Score	60	64.5
Normoweight -2 SD ≤ 2SD Z score	28	30.1
Overweight >2SD Z Score	5	5.4

of severe stunting by as much as 82.8%. The statistical test results obtained a p-value of 0.000, meaning that there is a significant relationship between the level of energy intake and the

incidence of stunting, from the results of the analysis there is a relationship between protein intake and the incidence of stunting in toddlers obtained that most of the protein intake is less in severe stunting toddlers by 83.5% and sufficient protein intake in severe stunting toddlers by 7.1%. The statistical test results obtained a p-value of 0.000, meaning there is a significant relationship between the level of protein intake and the incidence of stunting. The relationship between fat intake and the incidence of stunting shows that there is a relationship between fat intake and the incidence of stunting in toddlers, which is obtained that less fat intake in severe stunting

toddlers is 84% and sufficient fat intake in severe stunting toddlers is 22.2%. The statistical test results obtained a p-value of 0.000, meaning there is a significant relationship between the level of fat intake and the incidence of stunting. From the results of the analysis of the relationship between carbohydrate intake and the incidence of stunting in toddlers, it was found that most severe stunting children had less carbohydrate intake by 80% and sufficient carbohydrate intake in severe stunting toddlers by 47.8%. The statistical test result p-value is 0.001, meaning that there is a significant relationship between the level of carbohydrate intake and the incidence of stunting.

**Table 2.** Overview of nutrient intake

	Incidence of Stunting						Total		p-value
	Severe Stunting		Stunting		Normal		n	%	
	N	%	n	%	n	%			
Energy Intake									
Less	58	82.8	11	15.7	1	1.5	70	100	0.000
Sufficient	9	39.1	3	13.1	11	4.78	23	100	
Protein Intake									
Less	66	83.5	13	16.5	0	0	79	100	0.000
Simply	1	7.1	1	7.1	12	85.8	14	100	
Carbohydrate Intake									
Less	56	80	12	17.1	2	2.9	70	100	0.001
Sufficient	11	47.8	2	8.7	10	43.5	23	100	
Fat Intake									
Less	63	84	12	16	0	0	75	100	0.000
Sufficient	4	22.2	2	11.1	12	66.7	18	100	
Fe intake									
Less	58	80.5	13	18.1	1	1.4	72	100	0.000
Sufficient	9	42.8	1	4.8	11	52.4	21	100	
Omega 3 intake									
Less	56	78.8	13	18.3	2	2.9	71	100	0.000
Sufficient	11	50	1	4.5	10	45.5	22	100	
Zn intake									
Less	60	83.3	11	15.3	1	1.4	72	100	0.000
Sufficient	7	33.4	3	14.2	11	52.4	21	100	
Vitamin D Intake									
Less	58	80.5	13	18.3	1	1.4	72	100	0.000
Sufficient	9	33.4	1	4.5	11	52.4	21	100	
Ca intake									
Less	63	81.8	12	15.6	2	2.6	77	100	0.000
Sufficient	4	25	2	12.5	10	62.5	16	100	



**Table 3.** Relationship between micro and macro nutrient intake and the incidence of stunting

	Incidence of Stunting						Total		p-value
	Severe Stunting		Stunting		Normal		n	%	
	n	%	n	%	n	%			
Energy Intake									
Less	58	82.8	11	15.7	1	1.5	70	100	0.000
Sufficient	9	39.1	3	13.1	11	4.78	23	100	
Protein Intake									
Less	66	83.5	13	16.5	0	0	79	100	0.000
Simply	1	7.1	1	7.1	12	85.8	14	100	
Carbohydrate Intake									
Less	56	80	12	17.1	2	2.9	70	100	0.001
Sufficient	11	47.8	2	8.7	10	43.5	23	100	
Fat Intake									
Less	63	84	12	16	0	0	75	100	0.000
Sufficient	4	22.2	2	11.1	12	66.7	18	100	
Fe intake									
Less	58	80.5	13	18.1	1	1.4	72	100	0.000
Sufficient	9	42.8	1	4.8	11	52.4	21	100	
Omega 3 intake									
Less	56	78.8	13	18.3	2	2.9	71	100	0.000
Sufficient	11	50	1	4.5	10	45.5	22	100	
Zn intake									
Less	60	83.3	11	15.3	1	1.4	72	100	0.000
Sufficient	7	33.4	3	14.2	11	52.4	21	100	
Vitamin D Intake									
Less	58	80.5	13	18.3	1	1.4	72	100	0.000
Sufficient	9	33.4	1	4.5	11	52.4	21	100	
Ca intake									
Less	63	81.8	12	15.6	2	2.6	77	100	0.000
Sufficient	4	25	2	12.5	10	62.5	16	100	

From the results of the analysis of the relationship between Fe intake and the incidence of stunting in toddlers, it was found that most of the Fe intake was lacking in severe stunting children by 80.5% and sufficient Fe intake in severe stunting toddlers by 42.8%. The statistical test results obtained a p-value of 0.000, meaning there is a significant relationship between the level of Fe intake and the incidence of stunting. From the results of the analysis of the relationship between Omega 3 intake and the incidence of severe stunting in toddlers, it was found that most of the Omega 3 intake was less at 78.8%, and sufficient Omega 3 intake in severe stunting toddlers was 50%. The statistical test results obtained a p-value of 0.000, meaning there is a significant relationship

between the level of Omega 3 intake and the incidence of stunting. From the results of the analysis of the relationship between Zn intake and the incidence of stunting in toddlers, it was found that most of the Zn intake was less at 83.3% and sufficient Zn intake in severe stunting toddlers was 33.4%. The statistical test results obtained a p-value of 0.000, meaning there is a significant relationship between the level of Zn intake and the incidence of stunting. From the results of the analysis of the relationship between vitamin D intake and the incidence of stunting in toddlers, it was found that most of the vitamin D intake was less at 80.5%, and sufficient vitamin D intake in severe stunting toddlers was 42.8%.

**Table 4.** Relationships between micro and macronutrient intake and wasting incidence

	Incidence of Stunting						Total		p-value
	Wasting		Normoweight		Overweight		n	%	
	n	%	n	%	n	%			
Energy Intake									
Less	57	81.4	13	18.6	0	0	70	100	0.000
Sufficient	3	13	15	65.3	5	21.7	23	100	
Protein Intake									
Less	60	75.9	17	21.6	2	2.5	79	100	0.032
Sufficient	0	0	11	78.6	3	21.4	14	100	
Carbohydrate Intake									
Less	59	84.3	10	14.3	1	1.4	70	100	0.000
Sufficient	1	4.3	18	78.3	4	17.4	23	100	
Fat Intake									
Less	60	80	13	17.3	2	2.7	75	100	0.000
Sufficient	0	0	15	8.3	3	16.7	18	100	
Fe intake									
Less	58	80.5	13	18.1	1	1.4	72	100	0.000
Sufficient	2	9.5	15	71.5	4	19	21	100	
Omega 3 intake									
Less	60	84.5	9	12.7	2	2.8	71	100	0.000
Sufficient	0	0	19	86.4	3	13.6	22	100	
Zn intake									
Less	60	83.3	12	16.7	0	0	72	100	0.000
Sufficient	0	0	16	76.2	5	23.8	21	100	
Vitamin D Intake									
Less	57	79.2	13	18	2	2.8	72	100	0.000
Sufficient	3	14.3	15	71.4	3	14.3	21	100	
Ca intake									
Less	59	76.6	16	20.8	2	2.6	77	100	0.022
Sufficient	1	6.3	12	75	3	18.7	16	100	

The statistical test results obtained a p-value of 0.000, meaning there is a significant relationship between the level of vitamin D intake and the incidence of stunting. From the results of the analysis of the relationship between Ca intake and the incidence of stunting in toddlers, it was found that most of the Ca intake was less at 81.8% and sufficient Ca intake in severe stunting toddlers was 25%. The statistical test result p-value is 0.000, meaning there is a significant relationship between the level of Ca intake and the incidence of stunting.

**Table 4** shows the results of the analysis of the relationship between nutrient intake and the incidence of wasting in toddlers obtained that the lack of energy intake mostly affects the incidence of wasting as much as 81.4%. The statistical test results obtained a p-value of 0.000, meaning that

there is a significant relationship between the level of energy intake and the incidence of wasting, from the results of the analysis there is a relationship between protein intake and the incidence of wasting in toddlers obtained that most of the protein intake is less in toddlers wasting by 75.9%. The statistical test results obtained a p-value of 0.032, meaning there is a significant relationship between the level of protein intake and the incidence of wasting. The relationship between fat intake and the incidence of wasting showed that there was a relationship between fat intake and the incidence of wasting in children under five years of age, with 80% of children under five years of age having insufficient fat intake. The statistical test results obtained a p-value of 0.000, meaning that there is a significant relationship between the level of fat

intake and the incidence of wasting. From the results of the analysis of the relationship between carbohydrate intake and the incidence of wasting in toddlers, it was found that most of the carbohydrate intake was less at 84.3%, and sufficient carbohydrate intake in wasting toddlers was 4.3%. The statistical p-value was 0.000, meaning that there was a significant relationship between the level of carbohydrate intake and the incidence of wasting. From the results of the analysis of the relationship between Fe intake and the incidence of wasting in toddlers, it was found that most of the Fe intake was less at 80.5%, and sufficient Fe intake in wasting toddlers was 9.5%.

The statistical p-value was 0.000, meaning that there was a significant relationship between Fe intake and the incidence of wasting. There was a significant association between the level of Fe intake and the incidence of wasting. From the results of the relationship analysis, there was a significant correlation between Omega 3 intake and the incidence of wasting in children under five years old, with the majority of Omega 3 intake being less at 84.5%. The statistical p-value was 0.000, meaning that there was no significant relationship between the level of Omega 3 intake and the incidence of wasting. From the results of the analysis of the relationship between Zn intake and the incidence of wasting in toddlers, it was found that most of the Zn intake was less at 83.3%. The statistical p-value was 0.000, meaning that there was a significant relationship between the level of Zn intake and the incidence of wasting. From the results of the analysis of the relationship between vitamin D intake and the incidence of wasting in toddlers, it was found that most of the vitamin D intake was less at 79.2%, and sufficient vitamin D intake in toddlers with wasting was 14.3%. The statistical p-value was 0.000, meaning that there was a significant relationship between the level of vitamin D intake and the incidence of wasting. From the results of the analysis of the relationship between Ca intake and the incidence of wasting in toddlers, it was found that most of the Ca intake was less at 76.6%, and sufficient Ca intake in wasting toddlers was 6.3%. The statistical p-value was 0.022, meaning that there was a significant

relationship between the level of Ca intake and the incidence of wasting.

## Discussion

### *Relationship between energy intake and incidence of stunting and wasting*

The results of this study showed there was a significant relationship between the energy intake of toddlers with the incidence of stunting  $p=0.000$  ( $p<0.05$ ) and wasting  $p=0.000$  ( $p<0.05$ ).

The results of the study are in line with Husna<sup>13</sup> research which shows that there is a significant relationship of  $p=0.001$  ( $p<0.05$ ) between the level of energy intake and the incidence of stunting in toddlers. In addition, this study is also in line with the research of Syarfaini<sup>8</sup> which shows that there is a significant relationship of  $p=0.000$  ( $p<0.05$ ) between energy intake and the incidence of wasting in toddlers. Stunting and wasting are caused by the accumulation of deficiencies in the level of energy intake over a long period which ultimately causes the growth rate of children under five to be not optimal.<sup>14,15</sup>

Energy intake that does not meet the needs can cause energy imbalance. Prolonged energy imbalance leads to nutritional problems. Toddlers with low levels of energy intake affect the function and structural development of the brain and can result in stunted growth and cognitive development. Energy from food can be obtained from several macronutrients, namely carbohydrates, protein, and fat. Energy has a function as a support for the growth process, and body metabolism and plays a role in the process of physical activity.<sup>16,17</sup>

### *Relationship between protein intake and the incidence of stunting and wasting*

The results of this study indicate there is a significant relationship between the protein intake of toddlers with the incidence of stunting  $p=0.000$  ( $p<0.05$ ) and wasting  $p=0.032$  ( $p<0.05$ ). This study is in line with the research of Husna<sup>13</sup> and Syarfaini<sup>8</sup> which showed a significant relationship between protein intake with the

incidence of stunting ( $p=0.001$ ) and wasting ( $p=0.000$ ). Protein has a major role in growth in children under five. Protein intake is associated with effects on plasma levels of insulin growth factor I (IGF-I), bone matrix proteins, and growth factors, as well as calcium and phosphorus which play an important role in bone formation.<sup>18,19</sup>

#### *Relationship between carbohydrate intake and the incidence of stunting and wasting*

Based on statistical tests, shows that there is a significant relationship between carbohydrate intake and the incidence of stunting, where the p-value is obtained = 0.001 ( $p < 0.05$ ). This is in line with Ayuningtyas<sup>16</sup> in 2018, who obtained a value of  $p = 0.003$  ( $p < 0.05$ ) so there is a significant relationship between the level of carbohydrate intake and the incidence of stunting. This study also found a significant relationship between carbohydrate intake and the incidence of wasting  $p=0.000$  ( $p < 0.05$ ). This is in line with Soedarsono's research in 2021 which showed a value of  $p=0.014$  ( $p < 0.05$ ) in the relationship between carbohydrate intake and the incidence of wasting.<sup>20</sup>

Carbohydrates are the main energy provider and a relatively cheaper food source compared to other nutrients. If you experience a lack of carbohydrates the body will use fat and protein as a source of energy so that it will disrupt the balance of other nutrients that inhibit growth.<sup>17,21</sup>

#### *Relationship between fat intake and the incidence of stunting and wasting*

The results of this study indicate that there is a significant relationship between toddler fat intake and the incidence of stunting  $p=0.000$  ( $p < 0.05$ ), this is in line with research by Nur et al (2019) which obtained a value of  $p=0.000$  ( $p < 0.05$ ) in analyzing the relationship between the adequacy of fat intake and the incidence of stunting.<sup>22</sup>

The analysis of the relationship between fat intake and the incidence of wasting has the same results where the value of  $p=0.000$  ( $p < 0.05$ ) means that there is a significant relationship between the level of fat intake and the incidence

of wasting. This study is also in line with research by Diniyyah and Nindiya<sup>23</sup> in 2017 in Desa Suci Gresik, concluding that there is a significant relationship between fat intake and wasting nutritional status in children.

Fat intake from food if it is lacking, will have an impact on the lack of calorie or energy intake for the body's activity and metabolic processes.<sup>17</sup> Low-fat intake followed by reduced energy in the body will cause changes in muscle mass and body tissue and impaired absorption of fat-soluble vitamins.<sup>19,24</sup>

#### *Relationship between Fe intake and incidence of stunting and wasting*

The results of this study indicate there is a significant relationship between Fe intake of toddlers with the incidence of stunting  $p=0.000$  ( $p < 0.05$ ) and wasting  $p=0.000$  ( $p < 0.05$ ). The results of this study are in line with research conducted by Dewi and Nindya<sup>25</sup> and Bingan<sup>26</sup> where the results showed a significant relationship  $p=0.011$  ( $p < 0.05$ ) between the relationship between the level of Fe consumption adequacy with the incidence of stunting and wasting.

Stunting and wasting can occur due to chronic energy deficiency over a long period of years.<sup>27</sup> Iron intake is stored in muscle (myoglobin) and liver (ferritin). If iron sufficiency is inadequate, iron stores in the liver and spinal cord that are used to produce hemoglobin (Hb) decrease. Hb functions as an oxygen carrier from the lungs to the rest of the body. When Hb decreases, erythrocyte-free protoporphyrin will increase which will result in reduced heme synthesis and reduced erythrocyte size (microcytic erythrocytes). This condition will lead to iron anemia. In addition to causing iron anemia, iron deficiency can reduce the body's immune system, making it easier for infectious diseases to enter the body. Iron anemia and prolonged infectious diseases will affect the linear growth of the child.<sup>17,28</sup>

### *Relationship between Omega-3 intake and the incidence of stunting and wasting*

This study shows that there is a significant relationship between omega-3 intake and the incidence of stunting with a value of  $p=0.000$  ( $p<0.05$ ). This is in line with research conducted by Jutomo et al (2020) where the study found that 12 children with Omega-3 supplementation experienced a significant increase in height  $p=0.009$  ( $p<0.05$ ) [22]. This study also showed a significant relationship of  $p=0.000$  ( $p<0.05$ ) between the adequacy of omega-3 consumption and the incidence of wasting. This is supported by the research of Shahida Khan et al.,<sup>30</sup> which in their research mentioned that omega-3 supplementation increased the amount of energy consumed to improve the nutritional status of the respondents of the study.

Omega-3 PUFAs, EPA, and DHA are dietary essentials found mainly in fish and fish oil supplements. Consumption of omega-3 fatty acids can improve heart function and also function as an anti-inflammatory. Indirectly, omega 3 plays an important role in the growth and development of children under five. Long-chain polyunsaturated fatty acids including omega 3 are important for synaptogenesis, membrane function, and myelination. One form of omega 3 is docosahexaenoic acid (DHA), a neurobiological agent that affects neuronal membrane structure, synaptogenesis, and myelination. In lack of omega-3 fatty acids, the nerve cells in the brain will lack energy for nerve processes in the brain for growth and development which can interfere with the work and function of the brain. DHA functions as a nerve-wrapping tissue, this substance can launch commands to the nerves and deliver nerve stimuli to the brain.<sup>17,19,31</sup>

### *Relationship between Zn intake and the incidence of stunting and wasting*

Based on statistical tests, there is a significant relationship between Zn intake and the incidence of stunting  $p=0.000$  ( $p<0.05$ ) and a significant relationship with the incidence of wasting

$p=0.000$  ( $p<0.05$ ). The results in this study are in line with research conducted by Nur et al.,<sup>22</sup> in 2019, which in the study found a significant relationship with a value of  $p=0.004$  ( $p<0.05$ ) between Zn intake and the incidence of stunting.

Zn deficiency can reduce immunity and increase the risk of infectious diseases, leading to increased energy and zinc requirements which can inhibit bone growth. Zn is also one of the micronutrients related to protein and functions as a brain cell structure and neurotransmitters involved in brain memory so it can affect cognitive development.<sup>17,32</sup>

### *Relationship between Vitamin D intake and the incidence of stunting and wasting*

The results of this study indicate that there is a significant relationship between the level of vitamin D intake with the incidence of stunting  $p=0.000$  ( $p<0.05$ ) and the incidence of wasting  $p=0.000$  ( $p<0.05$ ). This is supported by research by Fakhira et al (2023) which shows the effect of vitamin D deficiency on the process of bone growth in stunted toddlers, namely the inhibition of IGF-1 function in increasing osteoblastogenesis to reduce the rate of bone growth to provide the conclusion that vitamin D has an important role in the process of calcium absorption which is useful for bone growth in stunted toddlers.<sup>17,19,33</sup> Other studies have also concluded that giving high doses of vitamin D as much as 200,000 IU can greatly help improve the results of Z-score body weight for height of children with severe malnutrition (wasting).<sup>34</sup> Another study also concluded the same results in severe acute malnutrition children who were given high-dose vitamin D3 supplementation in Pakistan.<sup>35</sup>

### *Relationship between Ca intake and the incidence of stunting and wasting*

The results of this study indicate there is a significant relationship between the level of Ca intake and the incidence of stunting  $p=0.000$  ( $p<0.05$ ) and wasting  $p=0.022$  ( $p<0.05$ ). This is in line with Wati's research (2021) where a



significant relationship was found ( $p=0.046$ ) between the adequacy of Ca intake and the incidence of stunting.<sup>36</sup> In a more in-depth study, it was mentioned that children with poor nutrition who experience Ca deficiency have a higher risk of death than children who do not experience Ca deficiency.<sup>37</sup> Micronutrients such as calcium play an important role in the linear growth of children. Optimal growth, especially bone lengthening, requires the intake of adequate amounts of animal protein and calcium.<sup>17,38</sup>

The concentration of calcium in the plasma, especially free calcium ions, is carefully maintained for the transmission of nerve impulses and muscle contraction, and as a catalyst for various biological reactions, such as the absorption of vitamin B12, the action of fat-splitting enzymes, pancreatic lipase, the secretion of insulin by the pancreas, and the formation and breakdown of acetylcholine. Calcium homeostasis is regulated primarily through an integrated hormonal system that controls calcium transport in the gut, kidneys, and bones. This process involves two major calcium-regulating hormones and their receptors namely PTH and PTH receptor, and 1,25(OH)<sub>2</sub>D and vitamin D receptor, as well as ionized serum calcium and calcium-sensing receptor. Serum calcium homeostasis develops to maintain extracellular levels of calcium ions within a normal range by circulating calcium to and from bone reserves.<sup>17,19,39</sup>

#### *Limitation of this study*

The limitation of this research is that it did not carry out a comprehensive analysis of other factors causing stunting and wasting, especially the history of the disease and the duration of the disease experienced by the subject. So it still cannot be determined with certainty whether it is only insufficient nutritional intake that influences the incidence of stunting and wasting.

#### **Conclusions**

The intake of energy, protein, carbohydrates, fat, iron, omega-3, zinc, vitamin D, and Ca is

significantly lower in children with nutritional problems (stunting and wasting) when compared with the RDA from the Indonesian Ministry of Health in 2019. Nutritional Problem such as stunting and wasting can be overcome with early warning through monitoring nutritional status by regularly measuring body weight and height at the posyandu so that it can be detected and provided with interventions including nutritional services and nutritional medical therapy according to the RDA to fulfill balanced nutrition. for toddlers optimally.

Recommended for further research to carry out optimal nutritional intake interventions to see whether there are changes before and after the intervention. It is also necessary to pay attention to other factors that cause stunting and wasting.

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## Association between consumption of ultra-processed foods and beverages with nutritional status of private senior high school students in Pontianak, West Kalimantan, Indonesia

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### Abstract

**Background:** Many low- and middle-income countries are now facing the “double burden” of malnutrition, one of them is overweight/obesity. Over 340 million children and adolescents were overweight and obesity in 2016. Obesity among adolescents may increase, in part due to changes in the food system, which now offers a wide range of ultra-processed foods (UPF) that minimize preparation time. Indonesia has also a large and rapidly growing market for unhealthy drinks, which are sold in various places including schools and hospitals.

**Objective:** This study aimed to investigate the association of UPF and beverages consumption and other related factors with nutritional status of senior high school students in Pontianak, West Kalimantan, Indonesia.

**Methods:** This cross-sectional study conducted in Pontianak investigated the association between UPF consumption and nutritional status of SHS students. Data collection was conducted at Imanuel and Petrus SHS Pontianak in June 2023, involving 273 students from grades 10th and 11th. Weight and height measurement was obtained for calculating the BMI for age Z-scores, while UPF and beverages consumption was obtained by FFQ. Structured questionnaire, 24-hours recall, and IPAQ-S were used for assessing sociodemographic status, Total Energy Intake and Physical Activity Level. Data analysis used SPSS version 26.

**Results:** The result found 40.3% of students were overweight-obesity; 51.6% consumed excessive UPF and beverages. It showed an inverse association between UPF consumption and nutritional status. The study identifies UPF and beverages consumption, gender, mother's education level, and family income as factors associated with nutritional status among adolescents.

**Conclusion:** The consumption of ultra-processed Foods was high, with the highest UPF intake came from snacks and sweets (22.4%). There was inverse association between UPF and beverages consumption with nutritional status. There was also significant association between UPF and beverages, gender, mother education level and family income with nutritional status.

**Keywords:** adolescent students, nutritional status, socio-demographic factors, sugar-sweetened beverages, ultra-processed foods

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## Introduction

Many low- and middle-income countries are now facing the “double burden” of malnutrition, one of them is overweight/obesity, particularly in urban settings. Over 340 million children and adolescents aged 5-19 were overweight and obesity in 2016.<sup>1</sup>

Obesity amongst adolescents is increasing due to changes in the food system, which now offers a wide range of ultra-processed foods (UPF) that minimize preparation time.<sup>2</sup> The term “ultra-processed food” was developed in a proposed new classification of foods known as the NOVA classification. These types of foods are not considered “real foods” and are created through a process that transforms food substances into ready-to-consume hyper-palatable products using additives. The NOVA classification involves 4 food categories, defined thus: group 1, unprocessed or minimally processed foods; group 2, processed culinary ingredients; group 3, processed foods; group 4, ultra-processed foods. The definition of ultra-processed food itself is industrial formulations typically with 5 or more and usually many ingredients. Besides salt, sugar, oils, and fats, ingredients of ultra-processed foods include food substances not commonly used in culinary preparations, such as hydrolysed protein, modified starches, and hydrogenated or interesterified oils, and additives whose purpose is to imitate sensorial qualities of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product, such as colorants, flavourings, non-sugar sweeteners, emulsifiers, humectants, sequestrants, and firming, bulking, de-foaming, anticaking, and glazing agents.<sup>31</sup> Ultra-processing makes these products highly profitable but also unhealthy. The classification group 4 of NOVA includes sugar-sweetened beverages (SSB) and fast food, which are frequently consumed by adolescents.<sup>3</sup>

Adolescents, who have independence in food choices, tend to eat out frequently and have busy schedules. They are the age group that is most exposed to UPF, which have high sugar, salt, and fat content, but low fiber and protein content.<sup>4,5</sup>

Indonesia has also a large and rapidly growing market for sugar-sweetened beverages, which are sold in various places including schools and hospitals.<sup>6</sup>

Low physical activity (PA) in youth is associated with a range of adverse health outcomes, however, relatively few adolescents meet physical activity guidelines. In addition, there is emerging evidence that sedentary behaviours in adolescence are negatively associated with adolescent health outcomes such as obesity and metabolic risk although the evidence for this using objective measures are inconsistent.<sup>32</sup>

Unfortunately, there are still lack of study that examine UPF consumption, especially those that separate food and beverages among senior high school students.

Based on the problems above, this study aimed to investigate the association between ultra-processed foods and beverages consumption and its association with nutritional status among senior high school students.

## Methods

This study was a cross-sectional investigation that assessed the association between consumption of Ultra-Processed Foods and beverages with nutritional status among senior high school students conducted in Pontianak, West Kalimantan.

This study obtained the ethical clearance from Ethical Committee Faculty of Medicine Universitas Indonesia with approval number: KET-786/UN2.F1/ETIK/PPM.00.02/2023.

The population of this study was the students at private senior high schools in Pontianak. The criteria of subjects were aged 15-17 years old and registered as a private SHS in South Pontianak in 2023, with the exclusion does not present at the time of data collection, sick at the time of data collection, on a diet (weight loss program) or consuming drinks or slimming drugs, and an athlete.

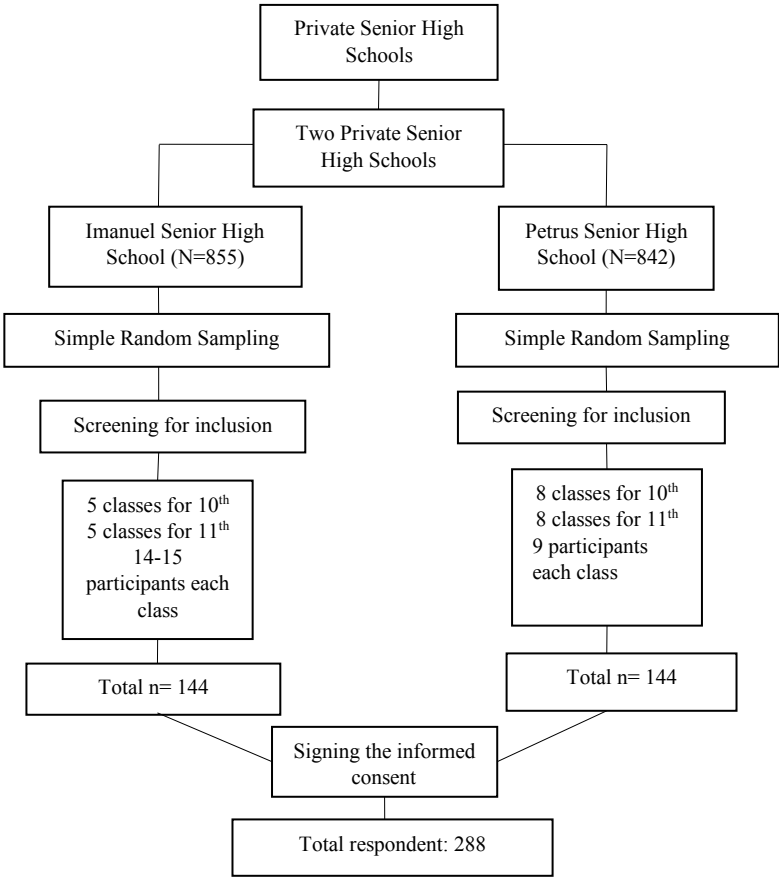
Based on data from the Ministry of Education (*Kemendikbud*) 2023, there are two private senior high schools that have the potential to be included



in this research. Schools’ selection was based on the largest number of students.

**Figure 1** shows the sampling procedure of this study. The sampling method used was simple random sampling. The sample calculation based on estimating two proportions with total calculation was 262, and to prevent the sample loss, so the total sample requires an additional 10% of sample, so the total sample was 288

respondents. The calculation comes up based on study from Qian Gan found that the prevalence of obesity that consume low sugar-sweetened beverages (<1 time/week) was 13.7%, and the prevalence of obesity that consume high sugar-sweetened beverages (1-<5 time/week) was 17.1%.<sup>33</sup>



**Figure 1.** Sampling procedure

The tools used in this study was anthropometric measurement for body weight measurement and height measurement, and questionnaires including General Questionnaire, 24-hours recall, FFQ, and IPAQ-S. Weight measurement was assess using body weighing scale of SAGA with the capacity 3 - 180 kg, and nearest scale of 0.1 kg. Before do the measurement, the tools had to be calibrated first to ensure the accuracy. This study used Multifungsi® as the tools to measure the height of respondents. This tool has the maximum measurement of 196.0 cm and an accuracy of 0.1 cm. Before measurements, all respondents were requested to remove any items they had on their bodies (e.g., jewellery, wallet, handphone, coins, watch, keys, accessories) that could potentially affect the accuracy of the measurements.

The respondents were asked to fill the general questionnaire about socio-demographic characteristics including name, date of birth, age, sex, school grade, body weight, height, nutritional status, parent's information (occupation, family income, level of education); and International Physical Activity Questionnaire Short Form (IPAQ-S) to measure the level of physical activity of students. The IPAQ-S measured physical activity over the last 7 days, covering four main physical activity domains: vigorous activity, moderate activity, and walking or low activity. To obtain the physical activity level, frequency and duration for each type of activity were calculated into Metabolic Equivalent of Task (MET). The duration of each activity, including walking, moderate-intensity activity, and vigorous-intensity activity, was computed to estimate the total amount of time spent in physical activity per week (MET-min/week).<sup>34</sup>

FFQ foods list will be list according to NOVA Classification group 4, based on the prior study conducted in Indonesia, and developed by market survey near schools' samples, and canteen in the schools' area survey. Respondents will be asked to their consumption in the last-7days based on the list of FFQ. Food frequencies questionnaire (FFQ) is to collecting frequency list of foods that consumed by students, to obtain a qualitative description of food consumption patterns. In this

study, the list of food and beverages based on NOVA classification were separated. The categorization of FFQ were categorized into two categories, normal ( $<$  median of total score), and excessive ( $\geq$  median of total score).

Respondents were asked for 24-hours recall form to collecting data of energy intake that consumed by students, to obtain the quantitative of food intake. In this study, the 24-hours recall form aims to identify the energy intake of respondent in 2 non-consecutive days (representative the weekday and weekend intake). All respondents were asked to mention all foods and beverages that they consumed in the last 24 hours from waking up in the morning until the night before going to bed. The enumerators repeated all the foods and beverages consumption to check the completeness of the data. Data from 24-hours recall was calculated in Nutrisurvey 2004 to get the amount of the energy intake of the respondents. The categorization of TEI were categorized into three categories, namely  $<80\%$  RDA,  $80-100\%$  RDA, and  $>100\%$  RDA.

In this study, physical activity will be assessed using International Physical Activity Questionnaire-Short Form (IPAQ-S) and calculated as metabolic equivalent (MET). For calculating the MET of respondent, first, all duration of vigorous, moderate, and light/walking activities in minute. Some activities will be including in vigorous, moderate, and light/walking level. For vigorous such as lifting heavy weight, digging, aerobics, fast cycling, soccer, futsal, basketball, jumping rope, swimming, tennis, badminton. For moderate level such as lifting light weight, cycling at normal speeds, household chores such as sweeping, mopping, jogging (excluding walking). Light/walking level such as work at home, walk to travel from place to place, and other walk that you have done solely for recreation, sports, exercise, or leisure. Physical activity level was categorized into three categories, low ( $< 600$  MET-minutes/week), moderate ( $600 - 2999$  MET-minutes/week), high ( $\geq 3000$  MET-minutes/week).<sup>34</sup>

The enumerators of this study have academic qualification was having complete a diploma or

bachelor from nutrition science, or students in final year majoring nutrition. Enumerators will be trained to increase their skills in the data collection during this study. All the questionnaires pretested to evaluate the flow of data collection, checking the understanding of the participants to answer the questionnaires, and ensure the validity of the questionnaires.

Additionally, the parent's education level was categorized into three categories, namely primary, secondary, and vocational. For parent's occupation category was categorized into three categories namely government, non-government, and unemployed. The family income was classified into two categorized; low (<IDR. 2.750.644,55, -) and high ( $\geq$ IDR. 2.750.644,55, -). The nutritional status calculated from weight (kg) divided by height squared (m<sup>2</sup>): kg/(m)<sup>2</sup>, and then the result of BMI will be plotted in the BMI-for-age percentiles grow chart from CDC based on age (years) and BMI. The result will be categorized as 4 categories. In further analysis, thinness and normal will be combined as non-obesity ( $-3$  SD -  $+1$  SD), and overweight and obesity will be combined as obesity ( $> +1$  SD -  $> +2$  SD).<sup>35</sup>

If all data was assured to be complete and the questionnaires were already fulfilled, the data was inputted into Microsoft Excel 2016 MSO. After that, all the data was processed using licensed IBM SPSS Version 26.0 for univariate, bivariate, and multivariate analysis. Chi-square test was used to determine whether there is a significant association between UPF and beverages and other confounding factors with nutritional status. Logistic regression was used for modelling the probability of a binary outcome based on the predictor variables.

Bivariate analysis was conducted between nutritional status and socio-demographic status; nutritional status and total energy intake; nutritional status and UPF and beverages consumption; and nutritional status and physical activity level. Factors which showed p-value less than 0.05 were considered as potential factors and included in multivariate analysis. In this study, multivariate analysis was conducted to analyse

the association between nutritional status and UPF consumption with several potential factors. The association between nutritional status and socio-demographic status was conducted to find potential factors that might influence the association between nutritional status and UPF consumption. Socio-demographic status consists of age, gender, father and mother educational level, father and mother occupation, family income, total energy intake and physical activity level.

## Results

During data collection, there were 288 students expected to participate. However, there were 4 students who did not come in the day of data collection, and 11 students did not complete the dietary data. Therefore, 273 students included as subjects for analysis.

**Table 1** shows that female and male students recruited in this study were comparable. Based on the educational level of the respondents' parents, most of father and mother of respondents had graduated from senior high school. Most of respondent's fathers were working in non-government area, while most of the mothers were housewives. More than 85% of the respondents had high family income i.e., above the regional minimum wage for Pontianak. Total energy intake of respondents was compared to the recommended dietary allowance (RDA) of Indonesia for age 15-18 years old in 2019 which was 2640 kcal/day for males and 2100 kcal for females. **Table 1** showed that 53.1% of the respondents had total energy intake more than 100% of RDA. Level of physical activity of the respondents in this study shows that 48.0% of them had moderate level.

In this study, Ultra-Processed Foods will be categorized into three categories; UPF and beverages were described as all foods and beverages that included in classification of NOVA classification group 4, UPF were described as all foods only, and Sugar-Sweetened Beverages were described as beverages only. **Table 2** shows that the median frequency of UPF and beverages consumption was 50 times consumed UPF in the

last 7-days, median of UPF for foods only was 35 times in the last 7-days, and median of SSB was 12 times consumed SSB in the last 7-days. The highest consumption of UPF and beverages of respondents of this study was 143 times of consumed UPF and beverages in the last 7-days.

Furthermore, **Table 2** showed that more than half of the respondents has excessive

consumption of Ultra-Processed Foods and beverages frequency. that 50.9% of the respondents has excessive of Ultra-Processed Foods consumption frequency. showed that 50.5% of the respondents has excessive of Ultra-Processed Foods consumption frequency.

**Table 1.** Characteristic of respondents based on sociodemographic (n=273)

Sociodemographic variables	n (%)
Age (year)	
15	31 (11.4)
16	154 (56.4)
17	88 (32.2)
Gender	
Male	135 (49.5)
Female	138 (50.5)
Father's educational level	
Elementary School	20 (7.3)
Middle School	32 (11.7)
High School	119 (43.6)
Vocational Education	102 (37.4)
Mother's educational level	
Elementary School	5 (1.8)
Middle School	84 (30.8)
High School	101 (37.0)
Vocational Education	83 (30.4)
Father's Occupation	
Government	29 (10.6)
Non-Government	232 (85)
Unemployed	12 (4.4)
Mother's Occupation	
Government	16 (5.9)
Non-Government	87 (31.9)
Unemployed	170 (62.3)
Family Income	
Low	40 (14.7)
High	233 (85.3)
Total Energy Intake	
<80% RDA	67 (24.5)
80-100% RDA	61 (22.3)
>100% RDA	145 (53.1)
Physical Activity Level	
Low	83 (30.4)
Moderate	131 (48.0)
High	59 (21.6)

<sup>1</sup>Educational level: Elementary School (graduated from Elementary School), Middle School (Junior High School), High School (Senior High School), Vocational Education (minimal Diploma level)

<sup>2</sup>Family Income: According to the regional minimum wage for Pontianak City 2023, IDR.2,750,644.55

<sup>3</sup>Physical Activity Level: Low (<600 MET), Moderate (600 – 2999 MET), High (≥ 3000 MET)

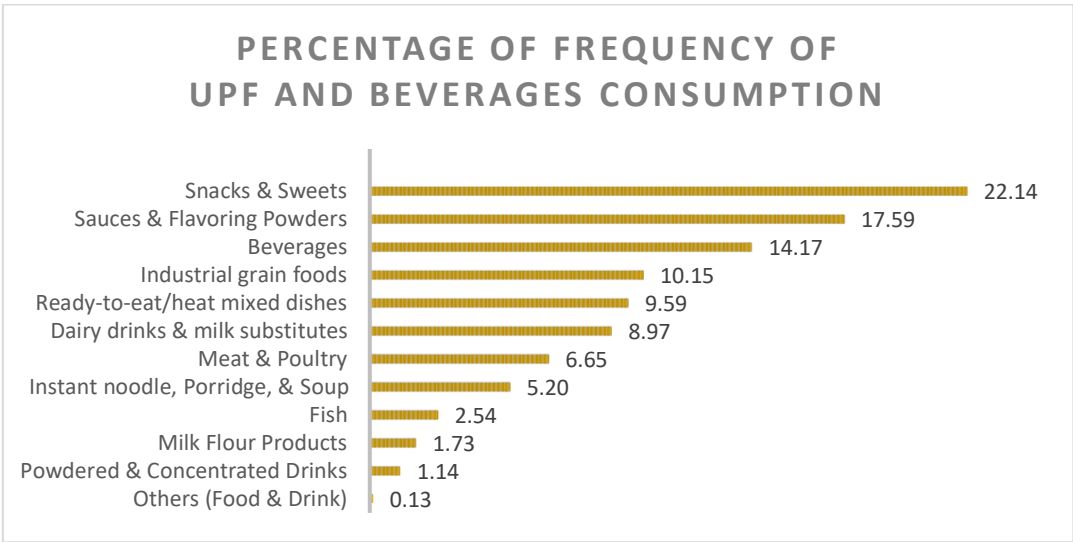
**Table 2** Frequency of all ultra-processed foods and beverages consumption of respondents (n=273)

Consumption	Median (Min-Max)	n (%)
UPF and beverages consumption	50 (11-143)	
UPF consumption	35 (8-107)	
SSB consumption	12 (1-50)	
UPF and Beverages consumption		
Normal		132 (48.4)
Excessive		141 (51.6)
UPF consumption		
Normal		134 (49.1)
Excessive		139 (50.9)
SSB Consumption		
Normal		135 (49.5)
Excessive		138 (50.5)

\*Consumption in the last 7-days

Nutritional status in this study was measured by BMI-for-age Z-Score (BAZ) assessment and then plotted in the grow chart by CDC for children and adolescents based on their gender. **Figure 2** shows the percentage of UPF and beverages consumption frequency based on the type of foods and drinks in the last 7-days. These types of foods refer to the food list from the FFQ of this study. The total percentage was obtained from the total frequency of UPF consumption, both food and drink, in the last 7-days. The highest percentage

frequency of ultra-processed foods consumption came from snacks and sweets for foods, and the highest percentage of frequency consumption of drinks came from beverages type such as electrolyte drinks, carbonated drinks, packaged drinks, while the lowest consumption frequency came from others from foods and drinks (e.g. protein powder and popcorn). **Table 3** shows that 40.3% respondents have overweight and obesity nutritional status.



\*Others Food and Drink (ea. protein powder, popcorn)

**Figure 2.** Percentage of frequency of ultra-processed foods and beverages consumption among respondents

**Table 3** Nutritional status of respondents (n=273)



Nutritional status	n (%)
Underweight	4 (1.5)
Normal	159 (58.2)
Overweight	99 (36.3)
Obesity	11 (4.0)

\*Underweight (-3 SD - < -2 SD), Normal (-2 SD - +1 SD), Overweight (+1 SD - +2 SD), Obesity (> +2 SD)

The association between nutritional status and UPF and beverages consumption was analysed in bivariate and multivariate analysis.

**Table 4** shows there was no significant association between age, father’s educational level, father’s occupation, and mother’s occupation with nutritional status ( $p>0.05$ ). The same results were also found in total energy intake and physical activity. Data on table 4.5 shown the association between total energy intake and physical activity were not significantly correlated with nutritional status ( $p>0.05$ ). But for gender, mother’s educational level and family income, there was an association to nutritional status ( $p\leq0.05$ ).

The association between Ultra-Processed Foods and beverages has a significant association with nutritional status ( $p\leq0.05$ ) on **Table 4**. While the association between Ultra-Processed Foods has not significantly associated with nutritional status ( $p>0.05$ ). The same result also shown at the association between Sugar-Sweetened Beverages has no significantly associated with nutritional status ( $p\leq0.05$ ).

Before conducting multivariate analysis, the researcher conducted multicollinearity analysis first. And the result shown that there is no multicollinearity found between UPF and SSB. Multivariate analysis is conducted to identify complex relationships between variables such as UPF and SSB consumption, nutritional status, and other potential factors simultaneously, to understand how these variables influence each other. In multivariate analysis after adjusted to other several confounders, UPF and beverages consumption, gender, mother educational level and family income were significantly correlated with nutritional status ( $p\leq0.05$ ). But for total energy intake and physical activity has no significant association to nutritional status. (**Table 5**).

## Discussion

Adolescents, though more advanced in physical and cognitive aspects, may exhibit behaviors inconsistent with adult norms. Girls had a higher participation ratio, aligning with gender-based differences in health-related awareness, potentially influencing increased participation in health research. Unlike national data, this study found a higher percentage of parents with senior high school education, differing from the educational trends in West Kalimantan.<sup>7-10</sup> This study found that the highest percentage of parent’s education was in senior high school. Most of respondent’s fathers were working in non-government area, while most of the mothers were not working.

Parents' education influences their occupation and impacts family income. In this study, over 85% of respondents had a family income exceeding the regional minimum wage for Pontianak in 2023 (Rp. 2,750,644.55). Adolescents from higher-income families were more likely to consume ultra-processed foods (UPF). High socioeconomic status emerged as a key factor in adolescent obesity, linked to increased media use, sedentary lifestyles, and exposure to appealing but nutritionally poor and energy-dense foods.<sup>11-13</sup>

Respondents' nutritional status is influenced by factors like total energy intake and physical activity. Total energy intake is shaped by age, gender, weight, height, and daily activities. The balance between calorie intake from food and beverages and energy expenditure through physical activities is crucial for maintaining energy balance.

**Table 4.** Association between socio-demographic factors and all ultra-processed foods and beverages with nutritional status (n=273)

Variables	Nutritional Status		p-value
	Non-Obesity	Obesity	
Age (year)			
15	17 (54.8)	14 (45.2)	0.735 <sup>a</sup>
16	91 (59.1)	63 (40.9)	
17	55 (62.5)	33 (37.5)	
Gender			
Male	66 (48.9)	69 (51.1)	0.000 <sup>a</sup>
Female	97 (70.3)	41 (29.7)	
Father's Educational Level			
Primary	30 (57.7)	22 (42.3)	0.858 <sup>a</sup>
Secondary	70 (58.8)	49 (41.2)	
Vocational	63 (61.8)	39 (38.2)	
Mother's Educational Level			
Primary	27 (30.3)	62 (69.7)	0.000 <sup>a</sup>
Secondary	85 (84.2)	16 (15.8)	
Vocational	51 (61.4)	32 (38.6)	
Father's Occupation			
Government	20 (69.0)	9 (31.0)	0.473 <sup>a</sup>
Non-Government	135 (58.2)	97 (41.8)	
Unemployed	8 (66.7)	4 (33.3)	
Mother's Occupation			
Government	11 (68.8)	5 (31.3)	0.603 <sup>a</sup>
Non-Government	49 (56.3)	38 (43.7)	
Unemployed	103 (60.6)	67 (39.4)	
Family Income			
Low	30 (75.0)	10 (25.0)	0.033 <sup>a</sup>
High	133 (57.1)	100 (42.9)	
Total Energy Intake			
<80% RDA	35 (52.2)	32 (47.8)	0.357 <sup>a</sup>
80-100% RDA	38 (62.3)	23 (37.7)	
>100% RDA	90 (62.1)	55 (37.9)	
Physical Activity			
Low	56 (67.5)	27 (32.5)	0.218 <sup>a</sup>
Moderate	73 (55.7)	58 (44.3)	
High	34 (57.6)	25 (42.4)	
UPF and beverages consumption			
Normal	69 (53.3)	63 (47.7)	0.015 <sup>a</sup>
Excessive	94 (66.7)	47 (33.3)	
UPF consumption			
Normal	73 (54.5)	61 (45.5)	0.084 <sup>a</sup>
Excessive	90 (64.7)	49 (35.5)	
SSB consumption			
Normal	74 (54.8)	61 (45.2)	0.103 <sup>a</sup>
Excessive	89 (64.5)	49 (35.5)	

<sup>a</sup>Chi-Square test;

Educational level: Primary (graduated from Elementary &amp; Junior High School), Secondary (graduated from Senior High School), Vocational (university level); Nutritional status: Non-Obesity (combine of underweight and normal status), Obesity (combine of overweight and obesity)

**Table 5.** Multivariate analysis between all processed foods and other potential factors with nutritional status (n=273)

Variables	B	t	p-value
UPF and Beverage's consumption	-0.124	-2.193	0.029*
Normal			
Excessive			
Gender	-0.167	-2.799	0.005*
Male			
Female			
Family Income	0.183	2.239	0.026*
Low			
High			
Mother Educational Level	-0.151	-4.261	0.000*
Primary			
Secondary			
Vocational			
Total Energy Intake	-0.024	-0.692	0.490
<80% RDA			
80-100% RDA			
>100% RDA			
Physical Activity			
Low	-0.006	-0.143	0.887
Moderate			
High			
Constant	1.869		

\*Significantly correlated; ENTER method; p-value in ANOVA = 0.000

Dependent variable: Nutritional status

Predictors (constant): UPF and beverages consumption, Gender, family income, TEI, PA

Higher physical activity levels lead to increased energy expenditure, emphasizing the importance of aligning calorie input with output.

In this study, most respondents had excessive energy intake (more than 100% of RDA) and moderate physical activity levels. Physical activity was assessed using IPAQ Short Form, differing from Riskesdas 2018, which used a modified GPAC from WHO.<sup>36</sup> The moderate activity levels may be attributed to prolonged sitting in class, though sports subjects contribute to energy expenditure. Additionally, reliance on vehicles for commuting reduces walking activities.

Ultra-processed foods (UPF) pose a global health concern due to their excessive calorie and sugar content. In this study, more than half of the adolescent respondents consumed excessive UPF, particularly in snacks and sweets. This trend is significant during the transition from childhood to adulthood, where individuals gain independence in choosing their food. In the USA, children's

diets consist of about two-thirds UPF, contributing to high body fat levels. High-income countries also witness UPFs constituting over 50% of daily energy intake, linked to unhealthy dietary patterns, overweight, and obesity. UPFs generally have lower nutritional quality, being high in energy, salt, sugars, and fats, while low in fiber and vitamins compared to unprocessed foods.<sup>13,14</sup>

Adolescents, particularly, favor sugary drinks, including soft drinks, sachet mixes, fruit drinks, cordials, flavored milks, cold teas/coffees, and energy/sports drinks. Consumption of these beverages is linked to dental issues and increases the risk of unhealthy weight gain, type-2 diabetes, gout, and non-alcoholic steatohepatitis. Indonesian school children spending 7 to 10 hours at school are prone to purchasing calorie-dense, nutrient-poor foods from school canteens, contributing to excessive consumption. Additionally, 50% of snack foods sold contain harmful chemicals in Indonesian schools.<sup>15,16</sup>

More than half of adolescents in this study had a normal nutritional status according to CDC categorization, aligning with similar findings in another study. Despite this, there were cases of overweight and obesity combined, with 40.3% falling into this category.<sup>17</sup> The percentage of obesity is comparable to normal nutritional status, signaling a potential increase in obesity cases among adolescents. Factors like consumption patterns, reduced physical activity, and frequent gadget use contribute to this trend. Globally, there has been a significant rise in pediatric obesity over the past five decades. Projections suggest that by 2030, around 254 million children and adolescents globally could be living with obesity, with several countries, including China, India, the USA, Indonesia, and Brazil, facing substantial burdens.<sup>18</sup>

Adolescence involves notable changes in physical and psychosocial development, impacting food choices. Greater independence and peer interactions often lead to a preference for calorie-dense fast foods. Sedentary behaviors, like increased screen time, may limit physical activity. Adolescents' heightened focus on appearance and psychological concerns further complicates dietary and lifestyle choices during this developmental period.<sup>19</sup>

Ultra-processed foods, rich in sugar, salt, and saturated fats, include items like soft drinks, breakfast cereals, reconstituted meat products, packaged breads, and ready-to-eat foods. A significant correlation between ultra-processed food (UPF) consumption and nutritional status was found through a chi-square test, consistent with research in Brazil associating UPF with obesity.<sup>20</sup> However, a study during the COVID-19 pandemic found no significant correlation between Body Mass Index (BAZ) and UPF consumption among school-aged children using ANOVA. The study utilized pre-pandemic data to maintain data quality and minimize bias due to the unavailability of direct offline data collection.<sup>21</sup>

Socio-demographic factors, including gender, play a role in nutritional status. Male students are more prone to consuming ultra-processed foods (UPF) and sugar-sweetened beverages (SSB), often due to habits like drinking energy beverages

after exercise or eating UPF while gaming.<sup>22</sup> CDC data shows that SSB consumption varies by age, sex, ethnicity, geography, and socioeconomic status, with higher prevalence among adolescent boys. Family, as the primary environment, significantly influences character formation. Maternal education levels impact health and nutritional risk, with lower education linked to challenges in accessing resources and information. Higher maternal education, while associated with greater family income, may contribute to increased UPF incorporation into meals. Household income affects dietary intake, with higher income leading to increased consumption of specific UPFs and SSBs. Additionally, adolescents' pocket money influences their UPF and SSB consumption, with higher allowances correlating with increased intake.<sup>23-26</sup>

Unlike findings in some high-income countries where ultra-processed foods (UPF) contribute over 50% to daily energy intake and are linked to unhealthy dietary patterns, this study reveals a reverse correlation between UPF consumption and total energy intake.<sup>27</sup> However, this discrepancy is attributed to a high level of underreporting of energy intakes, especially among overweight/obese adolescents. The underreporting may result from unconscious biases in misreporting unhealthy food intakes, leading to truthfully reported low food and energy intakes. In Brazil, UPFs' contribution to total energy intake has increased, replacing fresh foods, but this study's inverse correlation suggests potential data underreporting influenced by social desirability bias among adolescents. Mealtime irregularities and frequent skipping of meals may contribute to the underreporting phenomenon.<sup>28-30</sup>

The author is aware of this study's limitations and strengths. The study used a Food Frequency Questionnaire (FFQ) based on the Nova Classification group 4, modified for Pontianak City through market surveys. To enhance validity, enumerators, selected for their academic qualifications in nutrition science, underwent training and pre-testing with a sample similar to respondents. The pretesting helped refine instruments and reduce errors. Nutritional status

data collection instruments were calibrated, and steps were taken to minimize underreported data, such as excluding athletes and those on diets. Data collection occurred during school holidays, with a limited timeframe of 3 days per school due to final exams. Despite acknowledging limitations, the researcher took measures to mitigate errors and biases.

This study uniquely separates food and drinks in the classification of ultra-processed foods (UPF), providing distinct insights compared to research that often combines both. The findings have implications for school officials, offering valuable insights for creating regulations and programs aimed at enhancing the health of students. Educating adolescents about the impact of UPFs on nutritional status can empower them to make healthier choices. Programs can promote healthier eating habits and discourage excessive UPF consumption. Regulations may involve communities and families in nutritional awareness initiatives, fostering a comprehensive approach to improving dietary habits.

## Conclusion

In conclusion, this study focused on adolescents with a middle-upper socio-economic status. The findings revealed a high consumption of Ultra-Processed Foods, primarily from snacks and sweets (22.4%). Moreover, an inverse association was observed between UPF consumption, sugar-sweetened beverages intake, and nutritional status. Additionally, there was a significantly association between gender, mother's education level, family income, and nutritional status.

## Conflict of interest

Authors declared no conflict of interest regarding this article.

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## Overview of fluid and macronutrient intake, knowledge and attitudes and eating behavior among private university medical students in Jakarta

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### Abstract

**Background:** Adequate intake of micronutrients and fluids are important for study performance of students

**Objective:** To obtain an overview of macronutrient and fluid intake, also knowledge, attitudes, and healthy eating behavior of medical students from Krida Wacana Christian University (UKRIDA)

**Methods:** This is a cross sectional study conducted in October 2021 based on consecutive sampling. Height and weight was self-recorded, while the food and fluid intake was assessed via a phone interview using a 3-day diary. There were 97 students who met the inclusion and exclusion study's criteria who participated in macronutrient and fluid intake data, and 90 of them for the knowledge, attitudes, and healthy eating behavior data.

**Results:** As much as 10.3% of the study participants were underweight, 41.2% normal, and 48.5% overweight-obese. For macronutrient intake, compared to the RDA, 95.9% of subjects had inadequate energy intake, 100% had inadequate carbohydrates intake, 85.6% for fat intake and 55.7% for protein intake. For fluid intake, 76.3% of respondents had less, 18.6% had adequate, 5.1% had more than RDA. For the nutrition knowledge, 85.6% of respondents had good, 12.2% had sufficient, and 2.2% had inadequate nutrition knowledge. For the respondents' eating habits, 91.1% of respondents reported good, 7.8% adequate, and 1% non-healthy

**Conclusion:** Most of the subject had inadequate intake of energy, macronutrients, and fluids. Knowledge and attitudes towards healthy eating are mostly good, while healthy eating behavior can be further improved.

**Keywords:** Balance diet, food intake, medical student, knowledge-attitude-behavior

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## Introduction

Macronutrients are essential nutrients which consist of carbohydrates, proteins and fats which affect the nutritional status of a person. The 2018 National Report on Basic Health Research Results (Riskesdas) regarding nutritional status of those older than >18 years reported that 9.3% were thin, 55.3% normal, 13.6% overweight 21.8% obese.<sup>1</sup>

The Indonesian Regional Hydration Study (THIRST) 2009 reported that 46.1% of the population in Indonesia experienced mild dehydration.<sup>2</sup>

While a study among medical students from a public university in Yogyakarta, Indonesia reported a higher prevalence of dehydration of 60.9%.<sup>3</sup> Fluids are also the largest component of the body. Intake of fluids can come from food, drink and results of the metabolic process. In men, about 70% of their body weight is water, while in women, it is only around 60%.

The 2014 Indonesia Nutrition Guidelines recommend the composition of nutrients based on the type and amount of food according to the body's needs by taking into account the principle of food diversity.<sup>1</sup> The Indonesian recommended daily allowance (RDA) for 19-29 years old in 2019 is as follows: carbohydrates for men 430 g and women 360 g per day, protein: men 65 g and women 60 g per day, fat-men 75 g and women 60 g per day, fluid intake: men 2,500 ml and women 2,350 ml per day.<sup>4</sup>

Healthy eating behavior that can meet macronutrient and fluid intake is very important for young adults, including university students, who have various activities both academic and non-academic.<sup>5-7</sup> There are some expectations that university students, especially medical students, have a good knowledge and attitudes on nutrition knowledge which will be translated into healthy eating behaviour. However, there are only limited information is available for medical students in Indonesia. Thus the study aims to obtain an overview of macronutrient and fluid intake, also knowledge, attitudes, and healthy eating behavior of medical students from Krida Wacana Christian University (UKRIDA)

## Methods

This is a descriptive, cross-sectional study, conducted at the Faculty of Medicine and Health Sciences (FKIK) UKRIDA, West Jakarta in October 2021. The number of respondents was 97 based on the minimum required sample using formula for population proportion estimation. The respondents were selected based on a consecutive sampling method. The inclusion criteria were active medical students, aged 19-22 years, and signed informed consent. Exclusion criteria were fasting, participating in a weight loss program, experiencing eating disorders, being sick, having a history of illness, or circumstances requiring a certain dietary pattern.

Information about nutrient intake (energy, carbohydrate, protein, fat and fluid) was obtained via interviews using 3-day food and drink intake diary by data collectors who have been trained and supervised by the research team. Analysis of food intake was done using the NutriSurvey Software. The result of the calculation is the average intake of energy, carbohydrates, protein, fat and fluids consumed from the intake for 3 consecutive days. The outcome was then classified into insufficient: intake <80% of the 2019 RDA, sufficient: 80% - 100% and excess: >100%.

The data was collected via an online questionnaire on weight, height, body mass index (BMI), and knowledge, attitudes, and behavior on healthy eating. The BMI criteria were used based on World Health Organization (WHO) recommendations for the West Pacific region, as follows: underweight: BMI <18.5 kg/m<sup>2</sup>, normal: 18.5-22.9 kg/m<sup>2</sup>, overweight: 23-24.9 kg/m<sup>2</sup>, and obese: > 25 kg/m<sup>2</sup>.<sup>(8)</sup>

The results on knowledge and healthy eating behaviour are grouped into good: 76-100% of the answers are correct, adequate: 56-75%, and poor: < 55%.

The study protocol was approved by the Komite Etik Penelitian Medis dan Kesehatan Fakultas Kedokteran dan Ilmu Kesehatan Universitas Kristen Krida Wacana (UKRIDA) No. SLKE: 1185/SLKE-IM/UKKW/FKIK/KE/XI/2021

Results

There were 97 subjects who participated in the first data collection (energy, macronutrient, and fluid intake), of which 90 of them (93%) also participated in the second data collection

(knowledge, attitudes, and behavior regarding healthy eating) (**Table 1**).

**Table 2** shows the adequacy of dietary intakes compared to RDA. Furthermore, the subject’s knowledge, attitudes and behavior towards healthy eating is shown in **Table 3**.

**Table 1.** Participants’ characteristics

Variable	n (%) 97 (100)
Gender	
- Female	68 (70.1)
- Male	29 (29.9)
Residential	
- with parents/family	31 (32.0)
- without parents/family	66 (68.0)
Origin	
- DKI Jakarta	50 (51.5)
- Java-Bali	3 (3.1)
- Others	44 (45.4)
Meal allowance (Rp)	
- < 3.000.000/month	79 (81.4)
- ≥Rp. 3.000.000/month	18 (18.6)
Nutrition status based on BMI	
- Underweight	10 (10.3)
- Normal	40 (41.2)
- Overweight	16 (16.5)
- Obese	31 (32.0)



**Table 2.** Dietary intake (Energy, Macronutrient and Fluid) vs Recommended Daily Allowance (RDA) 2019

Variable	n (%) 97 (100)
Energy Intake	
- Inadequate	93 (95.9)
- Adequate	4 (4.1)
- Over	-
Carbohydrate Intake	
- Inadequate	97 (100.0)
- Adequate	-
- Over	-
Fat Intake	
- Inadequate	83 (85.6)
- Adequate	7 (7.2)
- Over	7 (7.2)
Protein Intake	
- Inadequate	54 (55.7)
- Adequate	25 (25.8)
- Over	18 (18.5)
Fluid Intake	
- Inadequate	74 (76.3)
- Adequate	18 (18.6)
- Over	5 (5.1)

**Table 3.** Knowledge, Attitude and Behavior on Healthy Eating

Variable	n (%) 90 (100)
Knowledge on Healthy Eating	
• Good	77 (85.6)
• Adequate	11 (12.2)
• Poor	2 (2.2)
Attitude on Healthy Eating	
• Good	82 (91.1)
• Adequate	7 (7.8)
• Poor	1 (1.0)
Behavior on Healthy Eating	
• Good	35 (38.9)
• Adequate	45 (50.0)
• Poor	11 (11.1)

## Discussion

From the demographic data, most of the research's participants were women, did not live with their parents/family and the amount of food allowance was less than Rp. 3,000,000/month. Most of them are coming from DKI Jakarta. This socio-economic status reflected by the place of residency and the allowance for food influences food intake and eating behavior, especially in developing countries.<sup>9-11</sup>

Based on the BMI of the study's participants, 60% of participated reported non-normal range either underweight or overweight/obese (**Table 1**). The percentage of participants who are overweight and obese was almost similar to those with normal-weight (48% vs 40%). The proportion of overweight and obesity in this study was higher as compared to those of 2018 RISKESDAS (Riset Kesehatan Dasar/National Health Survey) results (48% vs 38.5%, respectively). This could be due to differences in the BMI criteria used (BMI > 23 vs BMI > 25).<sup>8</sup> However, using BMI > 25, the proportion of overweight and obesity was almost similar (32%:35.4%, respectively). This high proportion of overweight and obese young adults, especially those with high education levels, needs special attention from various parties to prevent metabolic diseases in later life.

This study reported that the total energy intake was adequately met by almost all study participants (93%). (**Table 2**). However, all study participants had inadequate carbohydrate intake, and most of them had inadequate protein and fat intake. This, suggesting an imbalanced diet consumed by these students.<sup>5,12</sup> In addition, the Indonesian RDA was based on the reference values of average Indonesian people's height, weight and level of activities across wide areas of Indonesia.<sup>4</sup> Several studies have reported higher food intake among those living in urban compared to those in rural areas.<sup>13-15</sup> In addition, there are around 7% of study participants who have high fat intake. This could contribute to overweight and obesity in the future.<sup>16-17</sup> When compared between nutritional status based on BMI and energy intake based on the 2019 Indonesian RDA, there are inconsistent

results, namely most subjects have insufficient energy and macronutrient intake, but most subjects do not have normal BMI. This could be due to various reasons such as inaccuracy of recalling food intake from the interview,<sup>18,19</sup> or due to very low physical activity. In this study, no measurements of physical activity were carried out and no history of weight gain was recorded. As the study was conducted towards the end of COVID-19 pandemic, most people are still quite hesitant to go out and to do routine exercise, hence limiting the physical activity that they had.<sup>20,21</sup>

Most of the research subjects' fluid intake was inadequate. When compared with the THIRST national research and other local studies, the inadequate fluid intake in this study was much higher.<sup>2,3,22,23</sup>

Knowledge, attitudes, and behavior regarding healthy eating research subjects showed that most of them had good knowledge and attitudes, however, around 11% had poor eating behavior (**Table 3**). Thus, it seems that healthy eating behavior is not implemented despite having good knowledge and attitudes toward healthy eating behavior, which was similar with findings from other studies.<sup>7,24,25</sup> The support to increase adoption of good knowledge into healthy eating habits needs to get support from various parties, for example increasing the availability of balanced nutritional food in canteens, increasing health information, especially healthy eating behavior on-campus social media/communications.

Even though this study provides insights on nutritional status and understanding of healthy eating habits among young, educated adults which could be beneficial for other research in the future, there are some limitations such as analytical statistics to determine the relationship was not carried out. Thus, it is not possible to draw any associations between the variables. In addition, there is no information on the fiber intake and physical activity of the respondent which could provide more holistic insights. Last, the sample size for knowledge, behavior and attitude of healthy eating habits may not be sufficient as the minimum required sample was 97.

## Conclusion

Medical students from a private university in Jakarta had less energy, macronutrient, and fluid intake as compared to the RDA 2019. Although knowledge and attitudes on healthy eating were mostly good, their healthy eating behaviors can be further improved to have a better balanced diet.

## Conflict of interest

The authors declare that they have no conflict of interests.

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## LITERATURE REVIEW

### The role of polyphenols in atopic dermatitis: A literature review

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## Introduction

Atopic dermatitis (AD) is a chronic skin condition that may negatively impacts quality of life (QoL). Prevalence of AD has increased approximately three-fold in the last 30 years decades, with 15-30% of cases are found in children and 2-10% in adults.<sup>1</sup> This skin condition often appears in 3-4 months old babies and continues to develop until

## Abstract

**Background:** Atopic dermatitis (AD) is a chronic inflammatory skin with the appearance of pruritic eczema lesions, mostly found in young children, and impact their quality of life (QoL). In concordance with numerous treatment options, some adverse effect might. Recently, it has been discovered that polyphenols may provide satisfactory results for AD therapy and patient's QoL.

**Objectives:** This literature review objective to summarize recent research the use of polyphenols for AD therapy.

**Methods:** This is a literature review. Literature search was conducted in Pubmed, EBSCOHOST, Proquest, and Google Scholar, using keywords: "atopic dermatitis", "atopic eczema" and "polyphenols". Inclusion criteria were: 1) Randomized clinical trials, case reports, case series, literature reviews, systematic reviews, meta-analysis, cohorts, and experimental studies, 2) Available in full text, 3) Written in English, 4) Research studies with intervention conducted in human, 5) Research studies from early 2000s. While article with lack of available data is excluded. The author use Dermatology Life Quality Index (DLQI) to assess the role of polyphenols in QoL for AD.

**Results:** The use of polyphenols in AD shows satisfactory results through their antioxidant, anti-allergic and anti-inflammatory properties. Several studies have observed improvements in sleep disturbance scores, itchiness, and levels of skin moisture and elasticity levels in patients with AD.

**Conclusions:** Polyphenols use in AD provide satisfactory results in reducing symptoms that interfere with QoL. However, due to the limited number of studies conducted on human, further studies of larger-scale participants are needed to confirm the effect of polyphenols in AD treatment.

**Keywords:** atopic dermatitis, atopic eczema, polyphenols

the age of 2 years. Despite the exact mechanisms of AD pathogenesis remain unclear, several literatures suggest it is a result of combination between epidermal barrier dysfunction, immune dysregulation (increased inflammatory cells including monocytes, eosinophils, macrophages, mast cells, Th1 and Th2 cells), and environmental factors.<sup>3</sup>

Dermatological features of AD include itching, inflammation and erythema.<sup>2,3</sup> This symptoms is associated with QoL impairment such as the itching may affect mood and sleep hygiene, and the lesions may cause embarrassment, thus impacting on psychological wellbeing and social relationship.<sup>4</sup> Current therapeutic options generally consist of corticosteroids and

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antihistamines, however their long-term use potentially cause localized adverse effects including skin atrophy, telangiectasia, hypertrichosis, and dependence on topical steroids.<sup>2</sup> Therefore, several therapeutic options have emerged, such as polyphenols, probiotics, and vitamins that results in satisfactory findings.<sup>5</sup>

Polyphenols are substances that are widely distributed in variety of plants. The type of polyphenol content depends on the type of plant: isoflavones (soybeans), lignans (nuts and cereals), flavanols (tea, chocolate and apples), flavanones (citrus), flavonols (tea and apples), hydroxynamide acids (coffee, plums, and pears), quercetin (apples, grapes, and cherries), and anthocyanins (berries). Polyphenols play an important role in suppressing inflammatory processes and they have shown anti-oxidant, anti-microbial, anti-carcinogenic, neuroprotective, anti-allergic, anti-aging and anti-diabetic effects.<sup>6</sup> In this literature review, authors intend to further elaborate the role of polyphenols as AD therapy.

## Methods

This is a literature review. Literature search was conducted in Pubmed, EBSCOHOST, Proquest, and Google Scholar, using keywords: “atopic dermatitis” and “atopic eczema”. Inclusion criteria were: 1) Randomized clinical trials (RCT), case reports, case series, literature reviews, systematic reviews, meta-analysis, cohorts, and experimental studies, 2) Available in full text, 3) Written in English, 4) Research studies with intervention conducted in human. While article with lack of available data is excluded. The author uses Dermatology Life Quality Index (DLQI) to assess the role of polyphenols in quality life for AD.

## Discussion

### *Atopic Dermatitis*

Atopic dermatitis is a common, chronic, and often recurring condition. The incidence of AD has increased in recent decades, especially in developing countries.<sup>8</sup> Atopic dermatitis has

become a global health problem regarding its high-costs treatment, ability to negatively impact quality of life, and the resulting psychosocial distress. WHO estimates that AD affects 230 million people worldwide.<sup>9</sup> The prevalence in children ranges between 15-20%, while in adults it ranges between 1-10%. Globally, prevalence of AD has increased two to three-fold in recent decades.<sup>10</sup> The interaction between genetic, immune and environmental factors plays an important role in this increasing number of AD cases. Family history of atopic disease is a well-established main risk factor for the development of AD. In addition, other risk factors include low humidity, intake of foods with high sugar and unsaturated fats, repeated exposure to antibiotics before the age of five, and high social status.<sup>11</sup>

The pathogenesis of AD is complex, involving skin barrier disruption, dysregulation of the immune and cutaneous systems, dysbiosis of the skin bacterial microbiome, and genetic factors. Disruption of the skin barrier subsequently leads to chronic inflammation with epidermal hyperplasia and cellular infiltrates such as dendritic cells, eosinophils, and T cells. In the acute phase, Th2 cells produce IL-4, IL-5, IL-13, IL-25, and IL-31. Meanwhile, in the chronic phase, Th2 will be converted into Th1. Furthermore, there is a reduction of microbiota in AD, resulting in colonization by *Staphylococcus*, especially *S. aureus*, in 90% of patients with AD.<sup>11</sup> The clinical features of AD in the acute setting are acute eczema and wet pruritic lesions on dry skin. While, chronic AD consists of dry reddish or brownish lesions, cracked skin accompanied by lichenification, and prurigo nodularis. Pruritic skin especially at night may results in sleep disturbances which in turn weakens the body and may lead to mental health problems.<sup>8</sup>

There is no specific examination for AD apart from inspection of clinical features, however elevated serum IgE levels can be seen specifically in patient with AD. There are several criteria to help in diagnostic process, where criteria by Hanifin and Rajka and American Academy of Dermatology Consensus are the most widely used among those criteria.<sup>8</sup> The dry, itchy, and eczematous skin of AD has a profound impact on

QoL. The most commonly used tool is Dermatology Life Quality-Index (DLQI). DLQI assesses the impact of skin disease on symptoms and feelings, daily activities, leisure, work and school, personal relationships and the impact of treatment. DLQI score for AD patients ranges from 0 (no impact of the disease on QoL) to 30 points (extreme impact of the disease on QoL).<sup>13</sup>

### Polyphenols

Polyphenols are chemical substances that are widely found in plants. To date, thousands of types of polyphenols have been identified. Variety of plants have been identified containing polyphenols, including nuts, berries, grapes, tea, olives and lemons.<sup>13</sup> Polyphenols are divided into different groups according to the number of phenol rings they contain. Polyphenols are mainly classified into two groups, flavonoids and non-flavonoids. Flavonoids can be subdivided into different subgroups depending on the position of the hydroxyl group and on the basis of the structural features of the C ring. These subgroups are: flavanols, flavones, isoflavones, flavones, anthocyanidins, and flavanols. The carbon atoms of flavonoids are arranged in a C6-C3-C6 configuration with two aromatic rings bound to three carbon atoms, thus leading to the formation of an oxygenated heterocycle ring C. Flavonoids are found in variety of berries, grapes, tea, soybeans and onions.<sup>14</sup>

Non-flavonoids are further divided into phenolic acids, lignans and stilbenes. Phenolic acid is divided into two different classes based on the C1-C6 (benzoic) and C3-C6 (cinnamic acid hydroxy derivatives) groups. Phenolic acid is found widely in onions and berries. Lignans are plant secondary metabolites synthesised by oxidative coupling of two phenylpropane units and occur mostly in the free form, which are mostly found in flaxseed, sesame and sunflower seeds. Stilbene is also a small class of plant secondary metabolites derived from the phenylpropanoid pathway, some of which are associated with mechanisms of defence in the plant, found in many berries and nuts.<sup>15</sup> Dietary polyphenols are found in free form and/or bound

to polysaccharides and/or proteins. The process of absorption of flavonoids (except flavonols) in the small intestine are not well absorbed in the intestine, because they are highly hydrophilic to penetrate the walls of the digestive tract, resulting in fairly low bioavailability. Polyphenols that are not absorbed in the small intestine are able to reach the colon to help promote the growth of gut microbiota, such as *Lactobacillus* and *Bifidobacterium* which act as probiotics, thus finally reducing pathogenic microbes, such as *Clostridium histolyticum* and *Clostridium perfringens*.<sup>14</sup>

Process of polyphenol metabolism occurs in hepatocytes and enterocytes in the liver through phases I and II of biotransformation. Most of the dietary polyphenols are found in the form of ester bonds, glycosides, and polymers, where in these forms, they cannot be directly absorbed, where only about 5-10% of monomer form can be directly absorbed in the small intestine. This absorption process requires hydrolysis process assisted by digestive enzymes and gut microbiota. Alpha rhamnosidase, beta-glucosidase, and beta-glucuronidase are enzymes that aid the hydrolysis process. After the formation of aglycogens, they are then transferred to enterocytes via passive diffusion or through portal vein flow. Polyphenols are degraded with the help of gut microbiota into simple aromatic acids, followed by a conjugation process consisting of hydroxylation, methylation, sulfation and glucuronidation in liver cells to become O-glucuronate or O-sulfonate. Finally, it is then distributed throughout the organs and excreted in the urine.<sup>18</sup>

The bioavailability of polyphenols depends on the chemical structure of each type, where their bioavailability from highest to lowest in order are: isoflavones, flavonols, flavones, and anthocyanins.<sup>19</sup> In addition to the type of polyphenol, bioavailability also affected by food processing, interactions with other food ingredients, digestive enzymes, health conditions, and gut microbiota species.<sup>14</sup>

Polyphenols have multiple functions in lowering the symptoms of atopic dermatitis. Firstly, they act as antioxidant by inhibiting fat oxidation, decreasing hydroperoxide formation,

inhibiting ROS formation by inhibiting enzyme production, inducing the formation of antioxidant enzymes, regenerating alpha tocopherol and ascorbic acid, regulating transduction signal of the antioxidant defense system. Polyphenols stabilising free radicals and lower their reactivity.<sup>14</sup>

One has shown that quercetin has an antioxidant effect by preventing cell death secondary to oxidative stress in the keratinocyte layer, also other research have shown that quercetin 3-O-2-alpha-L-rhamnopyranoside inhibits apoptosis of keratinocyte by inhibiting caspase 8 and mitochondrial pathway. ROS (reactive oxygen species) is stimulated by NADPH oxidase as a messenger in several cellular signaling pathways, including NF kB and AP1 in inflamed skin. Transcriptional factor Nrf2 is released from the cytosolic protein Keap 1 into the nucleus, which then binds to transactive antioxidant enzyme genes. Activated Nrf2 facilitates phase II enzymes, such as HO-1. Studies in mice showed that Nrf2 loss results in high formation of NFkB including TNF-alpha, IL1b, and cyclooxygenase. Nrf2 is responsible for inhibiting regulation of HMGB1 to produce macrophage and/or monocyte. Quercetin have been proven effective in suppressing inflammatory process by activating Nrf2 signaling and inhibiting both NFkB and MAPK pathways.<sup>2</sup>

The second function of polyphenols against dermatitis is by reducing inflammatory process. Polyphenols inhibit enzymes that activate pro-inflammatory mediators, such as COX-2, LOX, iNOS, NF kB, activated protein-1 (AP-1), antioxidant phase II detoxifying enzyme activation, MAPK (mitogen activated protein kinase), protein kinase-C, and erythroid 2 related factor.<sup>19</sup> Quercetin suppresses proinflammatory cytokines in mast cells (NFkB and p38MAPK). Application of quercetin derivatives reduce inflammatory cytokines including IL-4, 5, 13, IgE, eosinophil and COX2 levels in mice with atopic dermatitis. HMGB1, RAGE, ERK1/2 NF kB act as inflammatory mediators that enhance proinflammatory cytokines in mice with atopic dermatitis. Quercetin inhibits proinflammatory

cytokines such as IL-1beta, IL-6, and TNF alpha and increases IL-10 levels.<sup>2</sup>

The role of polyphenols in allergic reactions works by inhibiting the production of signaling factors and cytokine; along with inhibiting gene expression in mast cells, basophils, and T cells. Polyphenols bind to allergen proteins, therefore turning them into insoluble proteins with lower potential. Among polyphenol structure, there are several potent components in inhibiting activation of pyrogallol allergic reactions, epigallocatechin gallate, a galloyl group in the benzene ring, and 2,3-cis configuration. One study found that quercetin significantly suppressed expression of inflammatory cytokines such as IL-4, IL-5 and NF kB in mice.<sup>16</sup>

#### *Effect of polyphenols on atopic dermatitis*

Skin is the largest organ of human body that is continuously exposed to the external environment. Inflammatory skin is caused by infiltration of T cells, mast cells, and eosinophils. Itching sensation is one of the most debilitating symptoms in AD that may affect the quality of life of patients in addition to precipitate complications including secondary infection. A study by Talamonti about quality of life using DLQI categorization, only two AD patients reported no negative influence of skin disease on their QoL, while 26 reported a small effect, 36 reported a moderate effect, and 110 reported a very large effect. As is commonly believed, the intense itching associated with AD often causes patients to experience severe sleep disturbances, leading to daytime sleepiness and sleep-related impairment. Sleep disturbances consequently results in functional impairment and profoundly worsens QoL for AD patients. It is also associated with unsatisfactory performance in school and work, reduced general health and safety, and considerable cost.<sup>17</sup>

Studies by Singh<sup>5</sup> suggest that inflammatory effects found in AD can be reversed with polyphenols use either as dietary intake or topical agents. Meanwhile, polyphenols act in inhibiting T cells production and inhibiting inflammatory cytokine, IL-2. Green tea extract contains

flavanols such as catechin and epicatechin. One of catechin derivatives – epigallocatechin galate (EGCG) – is an active substance found in green tea extract that has been shown to prevent inflammation of the skin layers. Catechin and EGCG are known to inhibit CD11b molecules binding into circulating T cells and B cells, thereby inhibiting their migration to areas of inflammation. EGCG also plays a role in inhibiting the release of histamine by mast cells and basophils, thus prevents IgE antigen complexes formation that potentially leads to allergic reactions. Photoprotective effect on the skin is observed with topical application. Moreover, green tea is also able to reduce hyperkeratosis and hyperplasia in inflammatory area of the skin.<sup>5,21</sup>

Avenanthramides, one compounds of polyphenol among many, which is predominantly found in wheat, are known to exert anti-inflammatory activity in the skin. This type of polyphenol works by inhibiting NF-kB activation and reducing pro-inflammatory cytokines such as TNF- $\alpha$  and IL-8. Furthermore, other forms of polyphenols such as Quercetin and Luteolin also have similar properties in reducing itchiness and redness caused by an elevated skin temperature. Evaluations conducted on topical application of Quercetin have shown to reduce irritation and improving the function of skin barrier. In addition to their anti-inflammatory properties, polyphenols also possess antioxidant effects. Consumption of high-dose cocoa drinks may help to maintain skin moisture and increase blood flow of cutaneous tissues. Lesional skin of patients with AD was more frequently colonized with *S. aureus*. Generally, antibiotics are used as treatment strategy for treating secondary infections. However, a study found that polyphenols may also inhibit enterotoxin activity from staphylococcal bacteria.<sup>5</sup>

A study by Kojima et al.,<sup>22</sup> assessed the benefit of apples containing polyphenols to treat allergies in patients with AD on 24 patients (10 patients in the control group and 14 patients in the ACT (Apples Condensed Tannin) group). This study includes participants with the age of 8-18 years, without any history of allergic rhinitis or bronchial asthma. The research was carried out for 10 weeks,

where they provided identical treatment between the 2 groups on the first 2 weeks using bufexamac ointment, half-doses of acemetasone dipropionate ointment, as well as the antihistamine hydroxyzine hydrochloride, given to each subject from the beginning to the end of the observation. Control group kept receiving the similar treatment given for those first 2 weeks. While the ACT group received ACT supplement 10 mg/kgBW/day divided into 2 doses for 8 weeks. Participants was monitored every 2 weeks to assess any lichenification, inflammation, cracking, itching, and sleep disturbance scores. Assessment of eosinophils, serum IgE, SGPT and SGOT were only performed at the beginning and the end of study period. This study concluded that there was no significant difference in terms of gender, age, serum IgE values, eosinophils, degree of AD, and duration of AD between control group and intervention group who received ACT. However, reduced inflammation, lichenification, and cracking scores were observed in the ACT group. Similarly, itching and sleep disturbance scores were also lower compared to the control group.

Additional study by Mehrbani<sup>23</sup> on using whey protein and *dodder* extract for AD patients was conducted on 52 patients with moderate to severe AD for 30 days. Moisture, elasticity, itchiness, sleep disturbance scores, changes in skin color, pH and skin sebum levels are all documented every 15 days. By the end of the study, 42 patients remained, 24 patients of dodder whey group and 18 patients of the control group. Final result of this study showed some significant differences of skin moisture level, skin elasticity, sleep disturbance scores, and itching in the group that received whey protein and dodder extract compared to control group. In terms of safety profile, there were 13 patients experienced anorexia and 4 patients with dyspepsia in the intervention group using whey dodder. However, blood pressure, kidney function, liver function, and body weight were not evaluated in this study.<sup>23</sup>



## Conclusion

Polyphenols may alleviate the symptoms presenting in patients with AD and improve their quality of life. Due to the limited number of studies in human, further studies involving larger-scale respondents are required to confirm the effect of polyphenols in AD treatment.

## Conflict of interest

Authors declared no conflict of interest regarding this article

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