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Associations between circulating fatty acid levels and metabolic risk factors

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HIGHLIGHTS

- Fasting fatty acids are unrelated to body fatness and insulin resistance in current participants.
- Some adverse features in the fatty acid profiles with respect to metabolic health.
- Fatty acid profiles may potentially be a tool to identify individuals at the risk of dyslipidemia.

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ABSTRACT

Circulating plasma fatty acids may play detrimental roles in metabolic health. Elevated fatty acid levels are always associated with obesity and type 2 diabetes (T2D). However, few studies have been conducted to examine the fasting plasma fatty acid profiles of healthy Asian populations with respect to obesity and metabolic health. In this study, we conducted a cross-sectional study of 172 healthy adults living in Singapore (age, 40 ± 14 y; 62 men). Our results show that no significant relationships between circulating fatty acid levels, obesity and insulin resistance were observed in current participants. While saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) elicited hypercholesterolemia effects, polyunsaturated fatty acids (PUFAs), especially omega-6, were hypocholesterolemic. Moreover, the most abundant fatty acids in the present participants included oleic acid (OA), palmitic acid (PA), stearic acid (SA), and linoleic acid (LA). While OA and SA were positively correlated with TG and TC, LA was negatively correlated with TG, TC, and LDL-C, but positively correlated with HDL-C. These results suggested that there are some adverse features in the plasma fatty acid profiles in present participants with respect to metabolic health. This information is useful in making dietary recommendations to provide the ideal fatty acid profiles that may reduce the cardiovascular risks of Chinese population living in Singapore.

1. Introduction

Circulating fatty acids have been proposed to be possible links between obesity, inflammation, insulin resistance, type 2 diabetes (T2D), lipid levels, and hypertension [1–5]. The putative role of fatty acids in obesity and insulin resistance has been studied over several decades with controversial results. An early observation suggested that plasma fatty acid concentrations would be increased in obese individuals due to increased fat mass [6]. The high levels of fatty acids may inhibit the anti-lipolytic action of insulin, leading to insulin resistance and further increases fatty acid releasing into the circulation [7]. Therefore, high levels of fatty acids are assumed to play a key role in the development of obesity-associated insulin resistance [8]. In contrast, fatty acid levels were found to contribute to insulin resistance independent of adiposity in a large cohort of Hispanic-Americans [9]. Nevertheless, there has been a steady accumulation of data recently showing that elevated fatty acid levels are not necessarily associated with body fatness and/or insulin resistance [10]. Therefore, the relationships between adiposity, fatty acids, and insulin resistance should be re-evaluated.

Meanwhile, circulating fatty acids have been shown to influence the total cholesterol (TC) and lipoprotein cholesterol concentrations, thus fatty acids have been regarded as a risk marker of cardiovascular

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diseases (CVDs) [11]. Over the years, numerous studies have shown that saturated fatty acids (SFAs) were hypercholesterolemic and that polyunsaturated fatty acids (PUFAs) were hypocholesterolemic [12,13]. These earlier studies, however, did not examine the effects of fatty acids on specific lipoproteins, which is important because of the opposing effects of low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) on CVD risks. Moreover, different kinds of fatty acids may paly diversified roles on carbohydrate and lipid metabolism. For example, a higher proportion of dihomo-γ-linolenic acid (DGLA) and palmitoleic acid was found to be metabolic markers associated with unhealthy obese individuals [14]. Some fatty acids, such as linoleic acid (LA) and linolenic acid (LNA), are not synthesized by human bodies and reflect dietary inakes. With realostic intakes of LA (< 13% of energy), OA and LA had similar effects of the serum lipoprotin profile [15,16]. Therefore, understanding the effects of these fatty acids on lipids and lipoproteins could provide information about the ideal fatty acid profile, which could be of public health significance. The results of these studies can also help to make dietary recommendations for the prevention and treatment of CVDs.

Since information is limited for fatty acid profiles in Asians with normal weight who show increased risk for insulin resistance and T2D, the goal of the current study was to determine the relations of fatty acid profiles with adiposity, insulin resistance and lipid levels among healthy adults living in Singapore in a cross-sectional study.

2. Methods

2.1. Study design

This study recruited 172 healthy Chinese adults: 62 men (36%) and 110 women (64%). They were recruited through advertisements on newspaper and posters that were placed around the National University of Singapore campus, public area and on the Clinical Nutrition Research Centre (CNRC) website. To be eligible, participants were required to be healthy Singaporeans or permanent residences who have resided in Singapore for at least five years. Participants were excluded if they were pregnant or diagnosed with any major diseases. Prior to the study, all participants were asked to restrict alcohol and caffeine-containing drinks as well as to refrain themselves from intense physical activity. All procedures involving human subjects were approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB, Reference Number: 2013/00783), Singapore.

2.2. Clinical measures

Participants arrived at the CNRC laboratory in the morning after a 10 h overnight fast. All participants gave written informed consent before starting. Two finger prick capillary blood samples were obtained for determining blood glucose concentration (FBG, mmol/L) using the HemoCue® 201 + RT Glucose analyzer (HemoCue Ltd, Dronfield, UK). In addition, a total of 10 mL of venous blood was collected into Vacutainers (Becton Dickinson Diagnostics, Franklin Lakes, NJ, USA). Blood samples were separated by centrifugation at 1500 rpm for 10 min at 4 °C within 2 h of being drawn and aliquots were stored at −80 °C until analysis. Fasting serum insulin (FSI, μU/mL) was measured using the immunochemistry analyzer COBAS e411 (Roche, HITACHI, USA). Insulin resistance index HOMA-IR was calculated from FBG and FSI using HOMA-IR = FBG × FSI/22.5. Fasting lipid parameters including TC, HDL-C, LDL-C, and triglyceride (TG) were measured using chemistry analyzer COBAS c311 (Roche, HITACHI, USA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an Omron blood pressure monitor (model HEM-907). The measurements were done in duplicate and readings were averaged. DEXA (QDR 4500A, fan-beam densitometer, Hologic, Waltham, USA, software version 8.21) was used for the measurement of fat mass (FM).

2.3. Plasma fatty acids analysis

2.3.1. Chemicals and reagents

Methanol (GC-MS grade), acetone (analysis grade), and iso-octane (GC-MS grade) were purchased from Merck Millipore (Singapore). Acetyl chloride (98%, reagent grade) and the external standard, Supelco 37 Component FAME mix containing fatty acid methyl esters (FAMEs) from C4 − C24 dissolved in dichloromethane were purchased from Sigma Aldrich (Singapore). Acetyl chloride in methanol (5%) was freshly prepared prior to each analysis.

2.3.2. Sample preparation

In each analysis, 50 μL of plasma was added into a 250 μL insert in a 2 mL vial with a screw cap. The auto-sampler added 150 μL of the derivatization reagent (5% acetyl chloride) and the sample was heated and mixed 3 times at 75 °C. The sequential heating and mixing steps were done 10 min apart during 30 min. The lipid fraction of the plasma is hydrolyzed and transmethylated into FAMEs. After which, 100 μL of the extraction solvent, i.e. iso-octane, was added. The sample was separated into 2 layers and FAMEs was located in the top layer [17].

2.3.3. GC-MS analysis

The analyses were performed using a 7890 GC system coupled to the 5977B mass spectrometer (MS) with the MassHunter software. The separation of the different fatty acids was done on a long polar HP-88 GC column (100 m × 0.25 mm, 0.2 μm, Agilent, USA). The GC oven was programmed at 50 °C for 1 min, heated to 175 °C at a rate of 15 °C/min, and then increased to 250 °C at a rate of 1 °C/min. The injection inlet was operated at split-less mode, 250 °C. Helium (He) was used as the carrier gas with a constant pressure of 322 kPa and the column flow was set at 2.14 mL/min at 50 °C [17].

2.3.4. Data quantification

Peak integration was done on the MassHunter Qualitative Analysis software B.07.01. We used the external standard FAME mix which was directly analyzed into the GCMS and used to determine the response and the concentration of the individual FAME.

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23. All data are expressed as means ± SD. One-way ANOVA was used for between-group comparisons. The strength of the association between fatty acids and clinical variables was assessed by linear regression of fatty acids on each variable separately. Two sided $p < 0.05$ was considered statistically significant in all cases.

3. Results

The general characteristics of the participants are presented in Table 1. There were no differences between men and women in mean ages ($p = 0.312$) and FM ($p = 0.315$). While men had significantly higher BMI, WC, BP, FBG, and TG than women, women had significantly higher HDL-C. In the present study, 26 fatty acids were identified (Table 2). There were no significant differences in the fatty acid levels between men and women (all $p > 0.05$).

The relationships between fatty acids, measures of obesity, and metabolic risk factors were shown in Table 3. It was observed that fatty acids were unrelated to body fatness after adjusting for gender and age (Model 1). After further adjusting for BMI (Model 2), both SFA and MUFA were significantly and positively correlated with WC, but total omega-6 was negatively correlated with WC. Table 3 shows that SFA correlated positively with TG, TC, LDL-C, and BP (Model 1 and Model 2). Similarly, MUFA correlated positively with TG, TC, and SBP, but correlated negatively with HDL-C. In contrast, total omega-3 showed

Table 1
Characteristics of the study population.

Variables	Total (n = 172)	Men (n = 62)	Women (n = 110)	p value[a]
Age (year)	39.6 ± 13.8	38.2 ± 13.9	40.4 ± 13.8	0.312
Height (cm)	164.2 ± 8.7	172.3 ± 7.1	159.6 ± 5.6	< 0.001
Weight (kg)	61.3 ± 12.9	71.0 ± 9.7	55.9 ± 11.1	< 0.001
BMI (kg/m^2)	22.6 ± 3.5	23.9 ± 2.8	21.9 ± 3.7	< 0.001
WC (cm)	75.0 ± 9.6	81.6 ± 7.7	71.2 ± 8.4	< 0.001
FM (kg)	19.4 ± 6.6	18.7 ± 5.7	19.8 ± 7.0	0.315
SBP (mmHg)	120 ± 15	127 ± 14	116 ± 14	< 0.001
DBP (mmHg)	74 ± 10	78 ± 11	72 ± 8	< 0.001
FBG (mmol/L)	4.5 ± 0.5	4.6 ± 0.5	4.4 ± 0.4	0.049
FSI (mU/L)	7.1 ± 4.2	7.2 ± 4.5	7.0 ± 4.0	0.718
HOMA-IR	1.4 ± 1.0	1.5 ± 1.1	1.4 ± 0.8	0.388
TG (mmol/L)	1.0 ± 0.5	1.1 ± 0.5	0.9 ± 0.5	0.020
TC (mmol/L)	5.2 ± 1.0	5.2 ± 1.0	5.2 ± 1.0	0.908
HDL-C (mmol/L)	1.6 ± 0.4	1.5 ± 0.3	1.7 ± 0.4	< 0.001
LDL-C (mmol/L)	3.3 ± 0.9	3.4 ± 0.9	3.3 ± 0.8	0.345
TFA (mg/L)	528 ± 229	543 ± 238	519 ± 225	0.505

Values are expressed as mean ± SD.
[a] One Way ANOVA.

negative correlation with TC. Total omega-6 correlated negatively with TG, TC, LDL-C, and BP, but correlated positively with HDL-C. No significant associations of fatty acids with FBG, FSI, and HOMA-IR were observed.

As shown in Table 2, the most abundant plasma fatty acid in the present participants was oleic acid (OA), followed by palmitic acid (PA), stearic acid (SA), and linoleic acid (LA). While OA and SA were positively correlated with TG (Table 4) and TC (Table 5), LA was negatively correlated with TG (Table 4), TC (Table 5), and LDL-C (Table 6), but positively correlated with HDL-C (Table 7).

4. Discussion

Elevated fatty acids in obese individuals were normally attributed to increased FM [6]. One possible explanation for the elevated fatty acids in obesity was that the enlarged adipose tissue mass released more fatty acids. Another possible reason is related with the reduced fatty acid clearance [18]. However, many studies in recent years have suggested that the differences between lean and obese are not so clearly observed. In the present study, we found that fatty acid levels were unrelated to body fatness (e.g. FM and WC) among healthy Chinese adults (mean BMI, 22.6 ± 3.5). The lack of association between fatty acids and measure of obesity was supported by a systematic review [10] and several large-scale epidemiological studies [19–21]. One may argue that the random fatty acids-obesity relationship is probably due to the altered day-to-day fatty acid levels within individuals. Magkos et al. [22] reported a good agreement between fatty acids measured on separate occasions (longer than 2 weeks). In another study, the correlation coefficient between two fatty acid measurements was 0.70 ($p < 0.001$) in 30 days [23]. These results suggest that there should be a clear within-person trend for fatty acid levels.

Elevated fatty acids compete with glucose as an energy source, it is therefore, always associated with decreased glucose oxidation and increased insulin resistance. In 1963, Randle et al. [24] reported that elevated fatty acids were associated with impaired sensitivity to insulin. After that, many studies have shown that higher fatty acid levels have been associated with increased risks of T2D and CVDs [25–27]. However, other studies reported contradictory results, showing that fasting fatty acids did not predict the development of metabolic syndrome (MetS) or T2D [28,29]. In our study, we did not observe any association between fatty acids and HOMA-IR. It should be noted that significantly positive association between HOMA-IR and FM ($r = 0.48$, $p < 0.001$) was present in the current participants. The body fatness-insulin resistance association is probably due to impaired adipose tissue fat storage or dysfunctional regulation of adipokines or adipose-related inflammatory cytokines instead of excessive fatty acids delivery from adipose tissue reported in the literature [5].

Table 2
Plasma fatty acid composition (% of total plasma fatty acids) of the study population.

Fatty acid	Total (n = 172)	Men (n = 62)	Women (n = 110)
SFA			
14:0 (Myristic acid)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
15:0 (Pentadecanoic acid)	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
16:0 (Palmitic acid, PA)	24.3 ± 1.9	24.5 ± 2.0	24.2 ± 1.8
17:0	1.3 ± 0.3	1.2 ± 0.3	1.3 ± 0.3
18:0 (Stearic acid, SA)	9.9 ± 1.3	10.0 ± 1.1	9.8 ± 1.4
20:0 (Arachidic acid)	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
24:0 (Lignoceric acid)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Total SFA	36.0 ± 2.1	36.3 ± 2.3	35.8 ± 1.9
MUFA			
14:1 (Myristoleic acid)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
16:1 c9 (Palmitoleic acid)	1.4 ± 0.3	1.3 ± 0.2	1.4 ± 0.3
17:1 c10	1.0 ± 1.0	0.9 ± 0.2	1.1 ± 1.2
18:1 c9 (Oleic acid, OA)	26.6 ± 3.2	26.8 ± 2.7	26.5 ± 3.4
18:1 t9 (Elaidic acid)	3.1 ± 0.7	3.0 ± 0.7	3.1 ± 0.6
20:1 c11 (Gondoic acid)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
22:1 c13 (Erucic acid)	1.9 ± 0.6	1.9 ± 0.6	1.9 ± 0.6
24:1 c15 (Nervonic acid)	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2
Total MUFA	35.0 ± 2.6	34.9 ± 2.2	35.0 ± 2.8
PUFA			
Omega-6			
18:2 c9c12 (Linoleic acid, LA)	8.8 ± 1.5	8.8 ± 1.5	8.9 ± 1.5
18:2 t9t12 (Linoelaidic acid)	1.4 ± 1.5	1.2 ± 1.2	1.5 ± 1.6
18:3 c6c9c12 (γ-linolenic acid, GLA)	0.8 ± 0.5	0.8 ± 0.5	0.9 ± 0.5
20:2 c11c14 (Dihomolinolenic acid)	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4
20:3 c8c11c14 (Dihomo-γ-linolenic acid, DGLA)	4.1 ± 1.2	4.3 ± 1.3	4.1 ± 1.1
20:4 c5c8c11c14 (Arachidonic acid, AA)	5.0 ± 1.4	5.1 ± 1.6	4.9 ± 1.3
22:2 c13c16 (Docosadienoic acid)	0.3 ± 0.2	0.3 ± 0.2	0.4 ± 0.2
Total omega-6	22.0 ± 3.2	21.9 ± 3.4	22.0 ± 3.1
Omega-3			
18:3 c9c12c15 (LNA)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
20:3 c11c14c17 (Dihomolinoleic acid)	1.5 ± 0.6	1.6 ± 0.6	1.4 ± 0.7
20:5 c5c8c11c14c17 (Eicosapentaenoic acid, EPA)	1.9 ± 0.5	1.8 ± 0.5	1.9 ± 0.5
22:6 c4c7c10c13c16c19 (Docosa-hexaenoic acid, DHA)	2.3 ± 0.6	2.2 ± 0.6	2.4 ± 0.6
Total omega-3	7.0 ± 1.6	6.9 ± 1.8	7.1 ± 1.6

Values are expressed as mean ± SD.
All $p > 0.05$, suggesting no significant difference in FATTY ACID levels between men and women.

Our results show that each fatty acid has its own effect on lipid metabolism. Myristic acid (14:0) significantly increased both total and LDL-C, while omega-3 fatty acids, especially eicosapentaenoic acid (EPA), have an inverse association. These findings are in agreement with previous findings [30,31]. A suggested mechanism for the TG-lowering effect of EPA is that the downregulation of genes involved in hepatic fatty acid synthesis and the upregulation of genes involved in hepatic β-oxidation. Thus, the availability of fatty acids for TG synthesis is decreased [32]. The higher content of EPA in the present participants may play a beneficial role in CVD risks. However, as reflected in the fatty acid profiles, the lower consumption of LA, but higher consumption of OA in the local population compared to Hong Kong Chinese and Caucasians may be detrimental with respect to CVD risks. Our findings agree with those of others [16,33], which indicate that LA lowers TC and LDL-C levels and raises HDL-C levels. In contrast with observations

Table 3
Multivariable-adjusted regressions analysis for fatty acid with variables of interest.

	SFA		MUFA		Omega-3		Omega-6	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
FM	0.09	0.08	0.08	0.07	−0.04	−0.03	−0.11	−0.09
WC	0.14	0.17*	0.14	0.17*	−0.09	−0.14	−0.15	−0.18*
FBG	−0.07	−0.08	0.07	0.06	−0.02	−0.01	−0.001	0.01
FSI	0.10	0.08	−0.03	−0.06	0.08	0.11	−0.09	−0.06
HOMA-IR	0.08	0.06	−0.02	−0.05	0.07	0.09	−0.07	−0.05
TG	0.27**	0.26**	0.19*	0.18*	−0.13	−0.13	−0.26**	−0.25**
HDL-C	−0.11	−0.09	−0.18*	−0.17*	−0.003	−0.02	0.22**	0.21*
LDL-C	0.18*	0.18*	0.08	0.08	0.01	0.02	−0.19*	−0.19*
TC	0.23**	0.24**	0.19*	0.20*	−0.18*	−0.19*	−0.21*	−0.22*
SBP	0.19*	0.18*	0.17*	0.17*	−0.07	−0.07	−0.23**	−0.22**
DBP	0.16*	0.15	0.14	0.13	−0.04	−0.03	−0.20*	−0.19*

*$p < 0.05$; **$p < 0.005$.
Model 1: Adjustment for age and gender.
Model 2: Model 1 added adjustment for BMI.

Table 4
Age-, gender-, and BMI-adjusted partial correlation coefficients between individual fatty acid and TG.

Fatty acid	R	p*
14:0	0.22	0.005
15:0	0.25	0.001
17:0	−0.16	0.040
18:0 (SA)	0.20	0.009
20:0	−0.20	0.008
14:1	0.29	< 0.001
18:1 c9 (OA)	0.20	0.009
18:1 t9	−0.17	0.029
20:1 c11	−0.19	0.012
18:2 c9c12 (LA)	−0.16	0.040
20:2 c11c14	−0.16	0.034
18:3 c9c12c15 (LNA)	−0.17	0.028
20:5 c5c8c11c14c17 (EPA)	−0.18	0.020

* Only $p < 0.05$ were reported.

Table 5
Age-, gender-, and BMI-adjusted partial correlation coefficients between individual fatty acid and TC.

Fatty acid	R	p*
14:0	0.34	< 0.001
15:0	0.27	< 0.001
17:0	−0.21	0.006
18:0 (SA)	0.25	0.001
20:0	−0.21	0.006
14:1	0.17	0.026
18:1 c9 (OA)	0.25	0.001
18:1 t9	−0.20	0.011
20:1 c11	−0.22	0.004
22:1 c13	−0.16	0.045
18:2 c9c12 (LA)	−0.17	0.025
20:2 c11c14	−0.22	0.004
18:3 c9c12c15 (LNA)	−0.21	0.006
20:5 c5c8c11c14c17 (EPA)	−0.21	0.007

* Only $p < 0.05$ were reported.

made by McDonald et al. [34], we found that circulating OA levels significantly increased TG and TC concentrations. This is probably because OA is the preferred substrate for the synthesis of TG and cholesteryl esters [35]. We acknowledge that although the correlations between individual fatty acids, TG, TC, LDL-C, and HDL-C were significant, the weak correlations were possibly due to the healthy status of our participants. Future studies will include unhealthy participants, allowing for the identification of correlations of fatty acids with biomarkers of health.

Table 6
Age-, gender-, and BMI-adjusted partial correlation coefficients between individual fatty acid and LDL-C.

Fatty acid	R	p*
14:0	0.20	0.010
24:1 c15	0.18	0.017
18:2 c9c12 (LA)	−0.23	0.003
20:3 c11c14c17	−0.16	0.034
20:4 c5c8c11c14 (AA)	−0.16	0.035

* Only $p < 0.05$ were reported.

Table 7
Age-, gender-, and BMI-adjusted partial correlation coefficients between individual fatty acid and HDL-C.

Fatty acid	R	p*
18:2 c9c12 (LA)	0.27	< 0.001

* Only $p < 0.05$ were reported.

Among the limitations of this study, the cross-sectional study design cannot be used to infer causation. The causal relationship between individual fatty acids and TG will need to be examined in both prospective and interventional studies. Moreover, this study did not include data regarding diet and physical activity. Because plasma fatty acid levels reflect food intake in weeks, they are more reflective of current dietary habits of individuals [36]. The generalizability of this study requires further replication in other populations but these data are the first step to elucidate the role of individual fatty acids in circulating lipid levels among individuals with normal weight. Further research is warranted, building upon the present results, to examine how very high or very low circulating fatty acid levels relate to chronic diseases.

5. Conclusions

In conclusion, the fasting plasma fatty acids are unrelated to body fatness and insulin resistance in the healthy Chinese adults living in Singapore. In contrast, excessive circulating of 5 SFAs, 3 MUFAs, and 1 PUFA were found to be related with TG levels. The associations between fatty acid and lipid levels attenuated by adjustment for gender, age and BMI. Therefore, we believe more prospective and interventional studies are needed to clarify the relationships between fatty acids, lipid levels, obesity, and insulin resistance. Clinical measurements of fatty acid profiles may potentially be developed into an alternative tool to identify individuals at the risk of dyslipidemia.

Conflicts of interest

We declare no conflict of interests.

CRediT authorship contribution statement

Xinyan Bi: Data curation, Formal analysis, Methodology, Project administration, Validation, Writing - original draft, Writing - review & editing. **Penny Liu Qing Yeo:** Formal analysis, Methodology, Writing - review & editing. **Yi Ting Loo:** Methodology, Project administration, Writing - review & editing. **Christiani Jeyakumar Henry:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing.

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