Special Article

A meta-analysis of studies examining associations between resonance Raman spectroscopy-assessed skin carotenoids and plasma carotenoids among adults and children

Stephanie B. Jilcott Pitts, Nevin S. Johnson, Qiang Wu, Gina C. Firnhaber, Archana Preet Kaur, and Justice Obasohan

Context: *No meta-analyses appeared to have been conducted to examine overall correlations between resonance Raman spectroscopy (RRS)–assessed skin carotenoids and plasma/serum carotenoids.* ***Objective:*** *To review the available literature and quantify the association between RRS-assessed skin carotenoids and plasma/serum carotenoids via a meta-analysis of observational studies.* ***Data Sources:*** *To identify relevant publications, we searched the PubMed, Embase, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ProQuest, and Scopus databases in April 2020 for items combining 3 concepts: Raman spectroscopy, skin, and plasma or serum.* ***Data Extraction:*** *Criteria for inclusion were publication in a peer-reviewed journal between 1990 and 2020, available in English language, and results reported as a baseline Pearson correlation coefficient. In teams of 2, the researchers independently reviewed titles and abstracts of 2212 nonduplicate papers with initial screening yielding 62 papers for full-text review, of which 15 were deemed eligible for inclusion.* ***Data Analysis:*** *A random-effects model in R (version 4.0.0) "meta" package was used to analyze the correlation between RRS-assessed skin and plasma/serum carotenoids. A subgroup analysis was conducted for studies involving adults and children, respectively.* ***Conclusions:*** *The 15 studies included 1155 individuals: 963 adults and 192 children. One study included children and adults. The random-effects model yielded an overall correlation of 0.68 (95%CI, 0.61–0.74;* $I^2 = 74\%$; $P < 0.01$*). The results were similar when grouped by adults and children. Among 963 adults, the correlation in the random-effects model was 0.69 (95%CI, 0.61–0.75;* $I^2 = 78\%$; $P < 0.01$*). Among 192 children, the correlation in the random-effects model was 0.66 (95%CI, 0.52– 0.77;* $I^2 = 55\%$; $P = 0.06$*). Overall, there was a positive, statistically significant correlation between RRS-assessed skin carotenoids and plasma/serum carotenoids in a pooled meta-analysis of 15 studies.*
Systematic Review Registration: *PROSPERO (record number 178835)*

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Key words: fruit and vegetable intake, plasma carotenoids, resonance Raman spectroscopy, serum carotenoids, skin carotenoids, validation.

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Table 1 **Description of the PICOS criteria used to define the research question**

Parameter	Description
Population	Included: adults and children Excluded: none
Intervention/correlation	Correlation with plasma or serum carotenoid levels
Comparison	Not applicable, because observational studies and correlations were reviewed, rather than interventions
Outcome	Resonance Raman spectroscopy–assessed skin carotenoids
Study design	Cross-sectional studies describing the correlation between skin and plasma or serum carotenoids

INTRODUCTION

Adequate fruit and vegetable consumption is associated with reduced risk of cardiovascular disease,[1,2] type 2 diabetes mellitus,[3] various cancers,[2,4] and obesity.[5] The *Dietary Guidelines for Americans* recommends inclusion of at least 2.5 cups of vegetables and 2 cups of fruits per day.[6] However, 9 in 10 Americans do not consume these recommended amounts.[7,8] Inadequate intake of fruits and vegetables may be partially responsible for the increase in the prevalence of obesity in the United States from 30.5% to 42.4% during the years 1999 to 2018.[9]

To more effectively promote population-level fruit and vegetable intake, improved measures of fruit and vegetable intake are needed.[10] Although self-reported measures of fruit and vegetable intake have predominated in studies, these measures are fraught with error, including recall bias and intervention-related bias.[10,11] Carotenoids are pigmented phytonutrients that occur naturally in many fruits and vegetables.[12] The most common dietary carotenoids found in human blood are α- and β-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin.[13] Carotenoids contribute to vital functions such as inhibiting tumor cell growth, serving as antioxidants, and protecting against eye disease.[14] Because of their predominance in fruits and vegetables, the current gold standard of measuring fruit and vegetable intake is measuring carotenoid levels in a blood sample.[13] However, collecting blood samples in field-based nutrition studies is challenging because of the need for a sterile environment, a trained phlebotomist, and blood processing in standard laboratory-based conditions. Because of these drawbacks, noninvasive yet valid methods are needed to assess fruit and vegetable intake. Skin carotenoid status, as assessed using resonance Raman spectroscopy (RRS), has emerged as a valid and reliable method to assess fruit and vegetable intake,[15,16] which overcomes many of the challenges related to obtaining plasma carotenoid measurements. RRS uses a small laser at a blue-light wavelength to assess carotenoid levels in the skin.[16,17] Researchers use RRS-assessed skin carotenoids as an indirect biomarker of total plasma/serum carotenoid levels, and as an as an objective measure of fruit and vegetable intake (eg, see *Shaping Healthy Choices Program*[18] and *Farm Fresh Foods for Healthy Kids*[19]).

Although there have been several studies examining associations between RRS-assessed skin carotenoids and plasma or serum carotenoids,[20] to date, to our knowledge, no meta-analyses have been conducted that examined overall correlations between RRS-assessed skin carotenoids and plasma/serum carotenoids. Thus, the aim of this study was to review the available literature and quantify the association between RRS-assessed skin carotenoids and plasma/serum carotenoids via a meta-analysis of observational studies. We hypothesized that RRS-assessed skin carotenoids would be positively associated with plasma/serum carotenoids across a variety of populations.

METHODS

In accordance with established PRISMA (Preferred Reporting of Systematic Reviews and Meta-analyses) guidelines, the prospective protocol for this systematic review was registered in PROSPERO (registration no. 178835). The PICOS (participants, interventions, comparisons, outcomes, and study design) criteria used to define the study question are listed in Table 1.

Literature search and review

For this systematic review, our goal was to identify and synthesize findings from published studies that included correlations between RRS-assessed skin carotenoid measurement (a proxy for fruit and vegetable intake) and serum or plasma carotenoid concentrations (the accepted standard measure of fruit and vegetable intake). To identify relevant publications, we searched the PubMed, Embase, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, ProQuest, and Scopus databases in April 2020 for sources combining 3 concepts: Raman spectroscopy, skin, and plasma or serum. Subject headings, which vary slightly by database, and keywords

were used to create concept searches, and searches were limited to title and abstract when possible. Search terms for RRS included spectrum analysis, carotenoid sensor, Raman spectrum measurement, Raman microscopy, and Raman spectroscopy. The terms skin, epidermis, epidermal, or dermal were used as to identify studies assessing skin. The terms blood, plasma, and serum were used to identify studies assessing plasma or serum levels. Searches for each concept were then combined using the Boolean operator AND. The search strategy was adjusted as needed between databases. The MEDLINE/PubMed search query used was: (((((((((“spectrum analysis”[MeSH] or “spectrum analysis, Raman”[MeSH])) or carotenoid sensor[title/abstract]) or Raman spectrum measurement[title/abstract]) or Raman microscopy[title/abstract]) or spectrum analysis[title/abstract]) or Raman spectroscopy[title/abstract] or Raman spectrometry[title/abstract])) and ((((((“skin”[MeSH]) or “epidermis”[MeSH]) or skin[title/abstract]) or epidermis[title/abstract]) or epidermal[title/abstract]) or dermal[title/abstract])) and ((((((“blood”[MeSH]) or “plasma”[MeSH]) or “serum”[MeSH]) or blood[title/abstract]) or plasma[title/abstract]) or serum[title/abstract]).

The structure of this search was guided by our experience with a previous systematic review,[20] during which including carotenoids as a search concept limited identification of studies. Criteria for inclusion were as follows: publication in a peer-reviewed journal between 1990 and 2020, available in English, and results reported as a baseline Pearson correlation coefficient between skin carotenoids as assessed by RRS and plasma or serum carotenoids.

Our combined database searches yielded 2980 items. Identified publications were loaded into Endnote 9.1 (Clarivate Analytics, Philadelphia, PA), where non–peer reviewed publications and duplicates were removed, leaving 2222 items. These remaining items were loaded into Covidence (Melbourne, Victoria, Australia), where 17 more duplicates were removed. Seven additional items were identified through reference lists of included items,[21] a Google Scholar search of author names from included items,[22] or from a document compiled by Pharmanex (Provo, UT)[23] listing papers associated with their Biophotonic Scanner.[24–28] A total of 2212 nonduplicate records were identified.

Initial review criteria included that the publication be an original work published in a peer-reviewed journal, reporting a validation study of Raman spectrum analysis including plasma/serum/blood carotenoid concentration as a comparison measure. Reports were excluded if they were not original works published in peer-reviewed journals and not available in English. Our review team consisted of 2 faculty members (S.B.J.P. and G.C.F.) and 3 research assistants (A.P.K., J.O., N.S.J.). At least one faculty member (either S.B.J.P. or G.C.F.) was involved in reviewing each item. After title and abstract screening, 62 reports remained. A total of 36 reports were excluded during full-text screening. Reasons for exclusion during full-text screening include the following: 17[29–45] did not meet inclusion criteria (eg, a review article, skin or plasma/serum carotenoids not assessed), 13 articles[46–58] and 3 abstracts from conference proceedings[59–61] used the wrong comparators (ie, devices other than RRS were used to assess skin carotenoids as compared with plasma/serum, or RRS-assessed skin carotenoids were compared with something other than plasma/serum), 1[21] provided a correlation that was cited from another included study,[24] ,1[62] had insufficient information (the authors stated a correlation was calculated but did not provide it in the text), and 1 was not available in English.[25]

Of the 26 remaining reports, 11 were excluded during data extraction. Reports excluded and reasons for exclusion during data extraction include the following: 6 abstracts[24,26–28,63,64] were from conference proceedings, which had insufficient data for the meta-analysis, 3[22,65,66] did not provide a correlation at baseline on an untransformed scale, 1[67] used remittance spectroscopy rather than RRS, and 1[68] provided a correlation that cited unpublished research. In total, 15 reports[15,69–82] were deemed as meeting criteria for inclusion in this review and meta-analysis (See Figure 1, PRISMA diagram).[15,21–82]

Two data extractors independently extracted the study reference, population characteristics (namely, age, sex, race, and body mass index, as available), sample size, statistical tests used to quantify the association between RRS-assessed skin carotenoids and plasma/serum carotenoids, and correlation or association outcomes. The data extractors came together to reach consensus on the data extracted from each article. The data were entered into an Excel spreadsheet (Microsoft, Redmond, WA) and analyzed.

Quality assessment

To measure the rigor of the studies, the Quality Appraisal Tool in Studies With Diverse Designs (QATSDD) was used as described by the developers.[83] The QATSDD includes 16 criteria. However, 4 criteria were considered not applicable for the purposes of this review. Two excluded criteria only apply to qualitative study designs, and 2 other criteria (theoretical basis and evidence of user involvement in design) were excluded because they were deemed not applicable to study designs examining validity of a research tool.

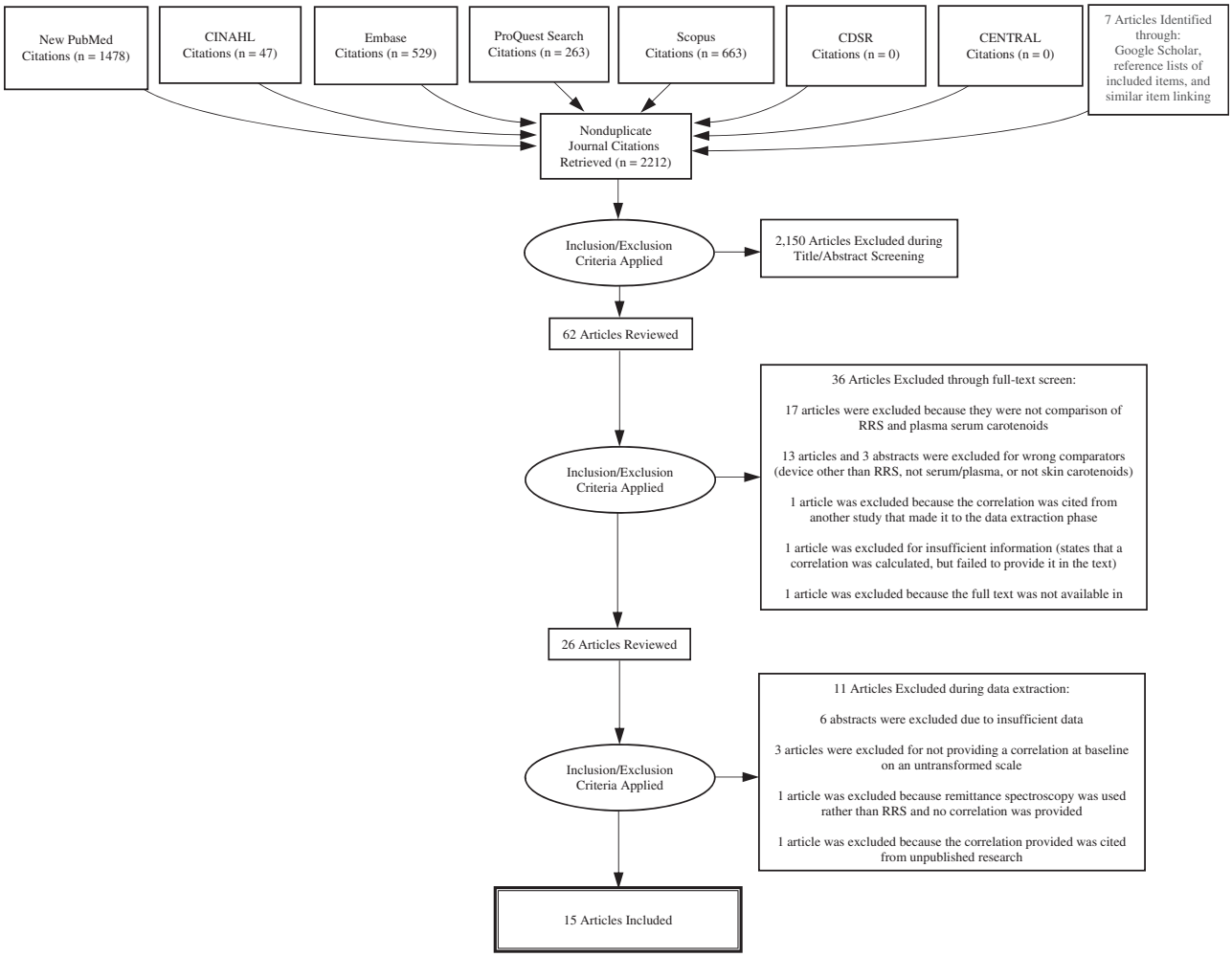

Figure 1 **PRISMA diagram for the meta-analysis of studies examining associations between resonance Raman spectroscopy-assessed skin carotenoids and plasma carotenoids among 963 adults and 192 children**. *Abbreviations:* CDSR, Cochrane Database of Systematic Reviews; RRS, resonance Raman spectroscopy

The following 12 criteria were evaluated for each study: statements of aims/objectives in the main body of the report; clear description of research setting; evidence of sample size considered in terms of analysis; representative sample of target group of a reasonable size; description of procedure for data collection; rationale for choice of data collection tool; detailed recruitment data; statistical assessment of reliability and validity of measurement tool(s); fit between stated research question and method of data collection; fit between research question and method of analysis; good justification for analytical method selected; and strengths and limitations critically discussed. For the purposes of this assessment, a "data collection tool" was defined as a method of data capture (eg, REDCap), and a "measurement tool" was defined as a validated scale or measurement device (eg, a food frequency questionnaire or Schorr Height Board). Each criterion was rated using a 4-point scale, ranging from 0 to 3, with 3 representing the highest quality. Two reviewers (A.P.K. and N.S.J.) independently analyzed and assigned a score to each of the included articles. The study team then discussed the independent findings and reconciled any scoring discrepancies. Each researcher justified their rating and shared the final assessment with the faculty researcher. Final quality scores for each article were calculated as a percentage by summing the points, dividing the sum by 36 (the maximum number of points), and multiplying that result by 100.

Statistical analysis

We used aggregate participant data and created a narrative (ie, descriptive) synthesis of all studies included. We used a random-effects model with the Sidik-Jonkman[84] estimator for the between-study heterogeneity variance to pool the overall correlation between RRS-assessed skin carotenoids and plasma/serum

Table 2 **Descriptive characteristics of studies included in the meta-analysis of validity of resonance Raman spectroscopy**

Reference	No. of participants	Pearson correlation coefficient	Mean age ± SD (years)a	Race/ethnicity, no. (%)	Biological sex, no. (%)	Mean BMI ± S (kg/m^2)	Plasma/serum, carotenoids assessed
Studies among adults							
Morgan et al 2019[76]	157	$r = 0.698$ $P < 0.0001$	58.56 ± 9.49	Non-Hispanic white: 150 (95.5) Other: 6 (3.8) Not reported: 1 (0.6)	Female: 157 (100)	Mean BMI: 35.72 ± 6.48	Serum: total carotenoids, specific carotenoids were not named.
Jahns et al 2019[77]	52	$r = 0.77$ $P < 0.001$	49.4 ± 0.8 (SE)	Non-Hispanic white: 50 (96)	Female: 52 (100)	Mean BMI: 26.5 ± 0.6 (SE) Overweight: 17 (33%) Obese: 12 (23%)	Plasma: α-, β-carotene, β-cryptoxanthin, lycopene and lutein/ zeaxanthin.
Rensburg et al 2016[79]	61	$r = 0.72$ $P < 0.001$	Overall population[a]: Males: 40.6 ± 12.2 Females: 42.8 ± 12.0	Overall population[a]: Non-Hispanic White: 78 (96.3) Indian: 1 (1.2) African: 2 (2.5)	Overall population[a]: Male : 19 (23) Female: 62 (77)	Mean BMI, males: 25.0 ± 2.2; females: 23.7 ± 2.7	Serum; lutein/zeaxanthin, β-carotene, lycopene.
Zidichouski et al 2009[80]	372	$r = 0.82$ $P = 0.001$	33.4 ± 10.0	Not provided	Male: 199 (53) Female: 173 (47)	Not provided.	Serum: α-, β-carotene, β-cryptoxanthin, l ycopene and lutein/ zeaxanthin.
Jahns et al 2014[78]	29	$r = 0.61$ $P < 0.001$	32.1 ± 2.5 (SE)	Non-Hispanic White: 28 (96)	Male: 9 (31) Female: 20 (69)	Mean BMI: 23.6 ± 0.6 (SE)	Plasma: α-, β-carotene, β-cryptoxanthin, lycopene and lutein/ zeaxanthin.
Bernstein et al 2012[81]	45	$r = 0.4727$ $P = 0.0010$	Overall population[a]: 77.4 ± 7.7 (range, 50–85)	Not provided.	Overall population[a]: Male: 24 (45) Female: 29 (55)	Not provided.	Serum: oxolutein, lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, and lycopene.
Henriksen et al 2013[71]	38[b]	$r = 0.63$ $P < 0.001$	Not provided	Mothers of normal-weight infants: Non-Hispanic White: 53 Latino: 43 Asian: 3 Mothers of infants with IUGR: Non-Hispanic White: 30 Latino: 60 Asian: 10	Female: 38 (100)	Not provided.	Serum: lutein, oxolutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, and lycopene.
Mayne et al 2010[15]	28	$r = 0.62$ $P = 0.006$	Overall population[a]: 37.0 (no SD reported; median: 33 y)	Overall population[a]: Non-Hispanic White: 62 (83.8) Non-White: 12 (16.2)	Overall population[a]: Male: 28 (38) Female: 46 (62)	Overall population[a]: Underweight: 4 (5.4%) Healthy weight: 45 (60.8%) Overweight: 20 (27.0%) Obese: 5 (6.8%)	Plasma: lutein, zeaxanthin, β-cryptoxanthin, β-carotene, and lycopene
Conrady et al 2017[82]	88	$r = 0.722$ $P < 0.0001$	59 ± 17 (range, 13–90)	Non-Hispanic White: 74 (84) African: 1 (1) Asian: 1 (1) Hispanic: 1 (1) Multinational: 1 (1) Not recorded: 10 (11)	Male: 39 (44) Female: 49 (56)	Not provided	Serum: lutein, zeaxanthin, lutein + zeaxanthin, and total carotenoids, specific carotenoids were not named

(continued)

Table 2 **Continued**

Reference	No. of participants	Pearson correlation coefficient	Mean age ± SD (years)a	Race/ethnicity, no. (%)	Biological sex, no. (%)	Mean BMI ± S (kg/m^2)	Plasma/serum, carotenoids assessed
Meinke et al 2010[74]	22	$r = 0.77$	Experimental group: 40.5 (range, 22–59; median, 42 y) Placebo group: 34.7 (range, 25–49; median, 29 y)	Not provided.	Experimental group: Male: 6 (54) Female: 5 (46) Placebo group: Male: 8 (73) Female: 3 (27)	Experimental group: 27.0 (range, 18–35; median, 29.1) Placebo group: 25.0 (range, 19–32; median, 26.1)	Serum: lutein, zeaxanthin, α-carotene, β-carotene, β-cryptoxanthin, and lycopene
Perrone et al 2016[75]	71	$r = 0.450$ $P < 0.0001$	Age range, 36–74	Not provided	Female: 71 (100)	27.06 ± 2.84	Serum: lycopene
Studies among children							
Aguilar et al 2014[69]	45	$r = 0.70$	10.5 (range, 5–17)	Non-Hispanic White: 34 (76) Hispanic: 7 (16) Asian: 3 (6) Pacific Islander: 1 (2)	Female: 25 (55) Male: 20 (45)	Underweight (<5th percentile): 4 (8%) Normal weight (5th to <85th percentile): 34 (76%) Overweight (>85th percentile): 7 (16%)	Serum: β-carotene, lycopene, and lutein
Bernstein et al 2013[70]	n = 37[c]	$r = 0.78$ $P < 0.0001$	Infants and children < 7 y	Non-Hispanic White: 30 (81.1) Hispanic: 4 (10.8) Multiracial: 3 (8.1)	Male: 16 (43) Female: 21 (57)	Not provided	Serum: total carotenoids, specific carotenoids were not named other than lutein/zeaxanthin
Henriksen et al 2013[71] (Infants: normal weight and IUGR)	N = 40*	$r = 0.39$ $P = 0.021$	Normal weight: gestational age: 37–38 wk: 43% 39–40+ wk: 57% IUGR: gestational age: 37–38 wk: 75% 39–40+ wk: 25%	Normal weight: Non-Hispanic White: 53 Latino: 43 Asian: 3 IUGR[c]: Non-Hispanic White: 33 Latino: 58 Asian: 8	Normal weight: Male: 53 Female: 47 IUGR: Male: 42 Female: 58	Birth weight <10th percentile for age: 10 (33.3%)	Serum: lutein, oxolutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, and lycopene
Ermakov et al 2013[72]	32	$r = 0.75$	Infants aged 1 d to 6 y	Non-Hispanic White: 32 (100)	Not provided	Not provided	Serum: total carotenoids, specific carotenoids were not named
Nguyen et al 2015[73]	38	$r = 0.62$ $P < 0.001$	11.2 ± 0.5 (range, 10–12)	Not provided	Male: 11 (29) Female: 27 (71)	BMI percentile ($\bar{x}$ + SD) 73.3 ± 26.3 Normal weight (5th to <85th percentile): 19 (50%) Overweight (85th to <95th percentile): 9 (23.7%) Obese (>95th percentile): 10 (26.3%)	Plasma: α-carotene, β-carotene, lutein, zeaxanthin, and lycopene

[a]Numbers given for the overall population but not for the subset of individuals for which both resonance Raman spectroscopy–assessed skin carotenoids and plasma/serum carotenoids were available.
[b]Control (healthy weight infants): 37 wk gestation or older: n = 30; IUGR: birth weight <10th percentile for age: n = 10. In this study, there were 2 sets of twins, so there are 38 mothers and 40 infants.
[c]All demographic data were obtained from supplementary materials found at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680006/bin/supp_13-11891_IOVS-13-11891-s01.pdf or https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3680006/bin/supp_54_6_4034__index.html.[70]
Abbreviations: BMI, body mass index; IUGR, intrauterine growth restriction.

Table 3 **Summary of methodological quality scores for 15 studies included in the meta-analysis of resonance Raman spectroscopy validity studies**

Criterion	Score (range: 0–3)														
	Morgan et al, 2019[76]	Jahns et al, 2019[77]	Aguilar et al, 2014[69]	Rensburg et al, 2016[79]	Zidichouski et al, 2009[80]	Jahns et al; 2014[78]	Bernstein et al; 2013[70]	Bernstein et al; 2012[81]	Henriksen et al; 2013[71]	Ermakov et al; 2013[72]	Nguyen et al; 2015[73]	Mayne et al; 2010[15]	Conrady et al; 2017[82]	Meinke et al; 2010[74]	Perrone et al; 2016[75]
Statement of aims/objectives in main body of report	2	3	3	3	3	3	1	1	3	1	3	3	2	3	2
Clear description of research setting	3	3	3	3	1	3	1	3	3	1	3	3	1	1	3
Evidence of sample size considered in terms of analysis	1	1	3	1	1	3	0	1	0	0	1	2	1	1	0
Representative sample of target group of a reasonable size	2	2	2	1	1	2	2	1	1	1	2	2	1	1	1
Description of procedure for data collection	3	3	3	2	2	3	3	2	3	3	3	3	2	2	2
Rationale for choice of data collection tool(s)	2	3	2	1	1	1	1	1	2	0	2	3	0	0	0
Detailed recruitment data	1	1	2	2	0	3	0	1	0	0	2	2	2	0	1
Statistical assessment of reliability and validity of measurement tool(s)	3	3	3	3	3	3	2	3	3	3	3	3	3	2	2
Fit between stated research question and method of data collection	3	2	3	2	3	3	3	3	3	3	3	3	3	3	2
Fit between research question and method of analysis	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2
Good justification for analytic method selected	3	3	3	2	3	3	1	2	2	2	3	2	1	2	2
Strengths and limitations critically discussed	2	3	2	2	1	3	1	2	2	0	2	2	2	0	0
Score total/maximum score possible; %	28/36; 77.8	30/36; 83.3	32/36; 88.9	25/36; 69.4	22/36; 61.1	33/36; 91.7	18/36; 50.0	23/36; 63.9	25/36; 69.4	17/36; 47.2	30/36; 83.3	31/36; 86.1	21/36; 58.3	18/36; 50.0	17/36; 47.2

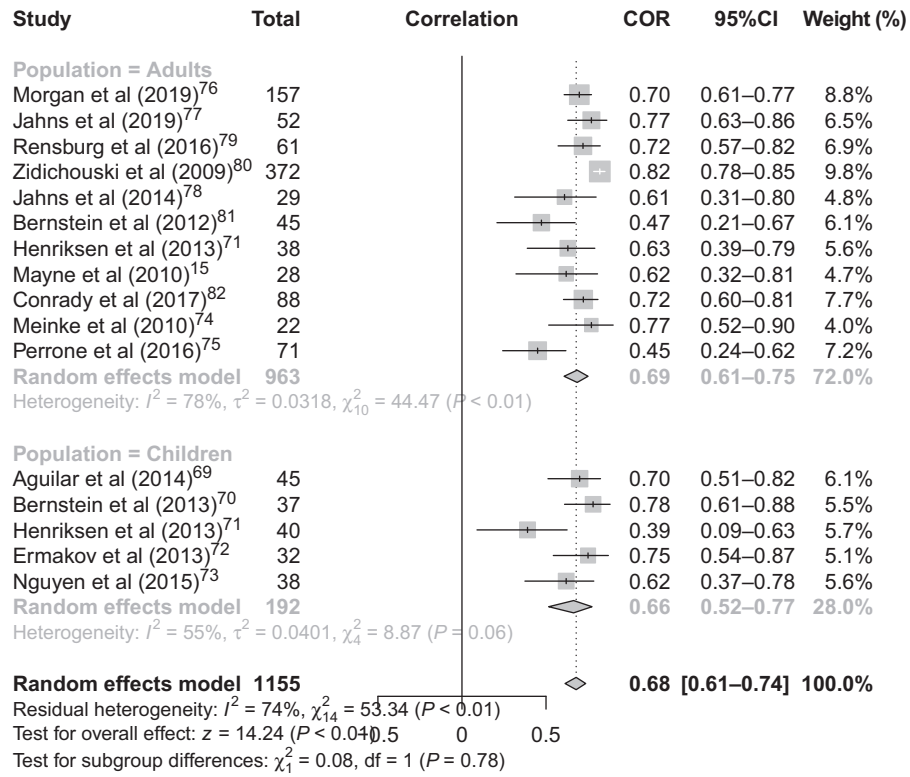

Figure 2 **Meta-analysis results for studies examining associations between resonance Raman spectroscopy-assessed skin carotenoids and plasma/serum carotenoids among 963 adults and 192 children.** *Abbreviations:* COR, correlation; df, degrees of freedom

carotenoids. In the analysis, Fisher z-transformation to the correlation was applied. The result was summarized in forest plots, and the Higgin and Thompson[85] heterogeneity index and Cochran Q test results were reported. Although some studies focused on adults, other focused on children. Thus, we conducted subgroup analysis to address the heterogeneity of the study effects due to age. To test the presence of publication bias, funnel plots were visually inspected and Egger tests[86] were provided. Statistical analyses were performed using R (4.0.0) software packages "meta" and "dmeta."

RESULTS

A synthesis of all studies is listed in Table 2.[15,69–82] There were 15 studies overall, with 5 including children[69–73] and 11 including adults.[15,71,74–82] One study[71] included both children and adults. Of the 11 studies among adults, 5 reported at least some participants from a racial/ethnic group other than non-Hispanic White,[15,71,76,79,82] and 2 reported including at least 10% of the sample from a racial/ethnic groups other than non-Hispanic White.[15,71] All the studies (100%) included information of participants' sex (4 studies included only females).[71,75–77] The mean ages ranged from 32 to 77 years. In 6 studies (54.5%), total plasma or serum carotenoid concentrations were measured[71,74,77,78,80,81]; 2 (18.2%) stated "total carotenoids" were used but did not specifically define total plasma/serum carotenoids[76,82]; and 3 (27.3%) included a subset of plasma/serum carotenoids, but not the total.[15,75,79]

Of the 5 studies among children,[69–73] 3 (60%) reported including at least 10% of the sample from a racial/ethnic groups other than non-Hispanic White,[69–71] and 4 (80%) included information on the participants' sex.[69–71,73] The mean ages ranged from gestation of 28 weeks to 12 years. One study (20%) used total serum carotenoid levels,[71] 2 (40%) stated "total carotenoids" were used but did not specifically define total plasma/serum carotenoids[70,72]; and 2 (40%) included a subset of plasma/serum carotenoids.[69,73]

The quality assessment is found in Table 3.[15,69–82] The scores ranged from 47.7% to 91.7%. The study by Jahns et al[78] received a score of 91.7% (highest); the studies by Ermakov et al[72] and Perrone et al[75] each received a score of 47.7%, the lowest of all of the studies. The average score for the studies was 68.3%. The 2 criteria that most studies scored highly on were (1) fit between stated research question and method of data collection criteria and (2) the fit between research question and method of analysis.

Figure 2[15,69–82] shows random-effects models for all studies. The random-effects model yielded an overall

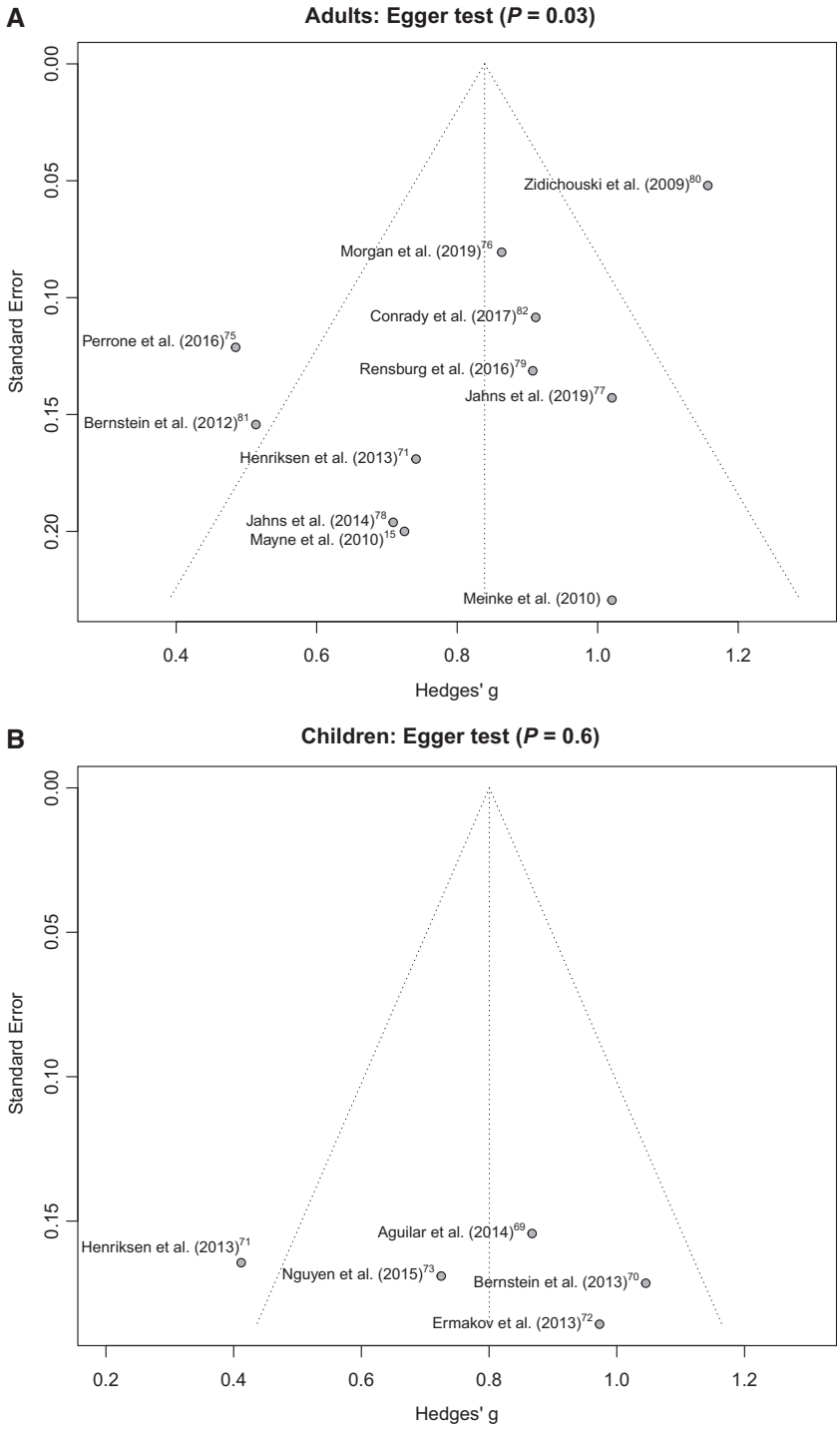

Figure 3 **Risk of bias assessment for studies examining the association between resonance Raman spectroscopy-assessed skin carotenoids and plasma/serum carotenoids among (a) adults and (b) children**.

Pearson correlation of 0.68 (95%CI, 0.61–0.74; I^2 = 74%; $P < 0.01$). The overall z-test of the pooled correlation was statistically significant ($P < 0.01$). The results were similar when grouped by adults and children. Among 963 adults, the correlation in the random-effects model was 0.69 (95%CI, 0.61–0.75; I^2 = 78%; $P < 0.01$). Among 192 children, the correlation in the random-effects model was 0.66 (95%CI, 0.52–0.77; I^2 = 55%; $P = 0.06$). The test for subgroup differences using Cochran Q was not statistically significant ($P = 0.78$). Funnel plots asymmetry and Egger test results showed the potential for publication bias among studies

involving adults ($P = 0.03$) but no evidence of publication bias of studies involving children ($P = 0.60$) (Figure 3a,b).[15,69–82]

DISCUSSION

This meta-analysis of studies examining the association between RRS-assessed skin carotenoids and plasma/serum carotenoids indicated a positive correlation between RRS-assessed skin carotenoids and plasma/serum carotenoids ($r = 0.68$; $P < 0.01$), and this was similar when comparing adults and children. RRS and other techniques to assess skin carotenoids are increasingly being used to evaluate public health nutrition interventions[18,19]; thus, the validity of such methods needs to be clearly established. In addition, the correlation between RRS-assessed skin carotenoids and serum carotenoids among infants in the Henriksen et al[71] study was relatively low ($r = 0.39$) and illuminates the complexity of perinatal maternal-infant physiology. More research is needed to assess the relationships between skin and plasma/serum carotenoids in mothers and infants. The results of our meta-analysis support the use of the RRS method for nutrition monitoring and evaluation of nutrition interventions. However, because only 5 of the included studies were among children,[69–73] and 4 studies included > 10% of the population from a non-White racial/ethnic group,[15,69–71] future studies should be conducted in populations of varying ages and racial/ethnic backgrounds, given the ultimate goal of evaluating interventions and policies to increase healthy eating among all populations.

Many factors affect carotenoid levels in the body, and each included study did not control for each possible factor. Extrinsic factors such as co-consumed lipids, food processing, molecular structure, medications, smoking, and alcohol have all been found to affect detection of plasma/serum carotenoids.[87] Intrinsic factors such as age, body composition, hormones variability, and genetics also play a strong role in carotenoid detection in serum and plasma.[87] Because these factors can also likely affect skin carotenoids, such factors should be considered in future validation studies of various skin carotenoid methods as an approximation of fruit and vegetable intake.

One of the strengths of this meta-analysis that we is examined overall correlations between RRS-assessed skin carotenoids and plasma/serum carotenoids; to our knowledge, this is the first meta-analyses to do so. It is noteworthy that all studies showed a positive correlation between RRS-assessed skin carotenoids and plasma/serum carotenoids, yet only 1 study examined the correlation between RRS-assessed skin carotenoids and skin biopsy specimens to confirm the validity of the skin RRS technique.[15] As reported earlier, the funnel plots and Egger test findings showed evidence of publication bias of studies in adults but no publication bias of studies among children.

A limitation of this study was that some of the studies solely focused on 1 or 2 carotenoids. Another limitation is that some studies used a longitudinal design, measuring skin and plasma/serum carotenoids at multiple time points and then examining correlations between these multiple time points. We were not able to include those data in this review, given the different statistical methods used in those analyses. An additional limitation is the medium to high heterogeneity in the studies, which was 1 reason we used random-effects models. This heterogeneity indicates the correlation may depend on each specific study population and could indicate publication bias or other forms of bias.[88]

CONCLUSION

The findings of this meta-analysis of 15 studies suggest RRS-assessed skin carotenoids can be used to approximate intake of carotenoid-rich fruits and vegetables. More research on the validity of measurement of skin carotenoids is warranted, particularly among individuals of different ages, as well as racially and ethnically diverse populations.

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Author contributions. S.B.J.P., G.C.F., and Q.W. conceptualized the study. G.C.F. conducted the systematic review and created the Covidence database. S.B.J.P., N.S.J., A.P.K., and J.O. conducted title, abstract, and full-text reviews; extracted study data, and created tables used for statistical analyses. Q.W. conducted all statistical analyses and created forest and funnel plots. G.C.F. and N.S.J. created the PRISMA diagram. N.S.J. and A.P.K. conducted the quality assessment. All authors contributed to the initial drafts of the paper. All authors reviewed and commented on subsequent drafts of the manuscript and approved the final version as submitted.

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