Association of desaturase activity and C-reactive protein in European children

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BACKGROUND: Desaturase enzymes influence the fatty acid (FA) composition of body tissues and their activity affects the conversion rate of saturated to monounsaturated FA and of polyunsaturated FA (PUFA) to long-chain PUFA. Desaturase activity has further been shown to be associated with inflammation. We investigate the association between delta-9 (D9D), delta-6 (D6D) and delta-5 desaturase (D5D) activity and high-sensitive C-reactive protein (CRP) in young children.

METHODS: In the IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) cohort study children were examined at baseline (T0) and after 2 y (T1). D9D, D6D, and D5D activities were estimated from T0 product-precursor FA ratios. CRP was measured at T0 and T1. In a subsample of 1,943 children with available information on FA, CRP, and covariates, the cross-sectional and longitudinal associations of desaturase activity and CRP were analyzed.

RESULTS: Cross-sectionally, a D9D increase of 0.01 units was associated with a 11% higher risk of having a serum CRP ≥ Percentile 75 (P75) (OR, 99% CI: 1.11 (1.01; 1.22)) whereas D6D and D5D were not associated with CRP. No significant associations were observed between baseline desaturase activity and CRP 2 y later.

CONCLUSION: Cross-sectionally, our results indicate a positive association of D9D and CRP independent of weight status. High D9D activity may increase the risk of subclinical inflammation which is associated with metabolic disorders. As D9D expression increases with higher intake of saturated FA and carbohydrates, dietary changes may influence D9D activity and thus CRP. However, it remains to be investigated whether there is a causal relationship between D9D activity and CRP.

Moderately increased C-reactive protein (CRP) is a marker of subclinical inflammation which is frequently observed in obese subjects and was shown to be predictive for cardiovascular diseases (1). As obesity rates have dramatically increased also in young age groups (2,3), increased CRP is already prevalent in children (1). Inflammatory status is related to the fatty acid (FA) tissue levels and to dietary FA intake (4,5). FA composition of body tissues strongly depends on dietary intake of FA and on the activity of the enzymes involved in the conversion of saturated FA (SFA) to monounsaturated FA (MUFA) and of polyunsaturated FA (PUFA) to long-chain (LC) PUFA, i.e., desaturase and elongase enzymes.

Delta-9 desaturase (D9D, also called stearoyl-CoA desaturase, SCD) catalyzes the desaturation of SFA, preferably palmitic (16:0) and stearic acid (18:0), to the MUFA palmitoleic (16:1n-7) and oleic acid (18:1n-9). It is the rate-limiting enzyme and therefore influences the body composition of these FA. Delta-6 desaturase (D6D) catalyzes the first step in the conversion of the n-6 PUFA linoleic (18:2n-6) and the n-3 PUFA α-linolenic acid (18:3n-3) to the LC PUFA arachidonic (20:4n-6) and eicosapentaenoic acid (20:5n-3). This step is followed by elongation of the intermediate PUFA and by subsequent desaturation of these intermediates by delta-5 desaturase (D5D) to the abovementioned LC PUFA. Linoleic acid and α-linolenic acid cannot be synthesized and must be supplied by the diet. D6D and D5D are the rate-limiting enzymes for the desaturation steps in the conversion from the essential n-6 and n-3 precursor PUFA to the LC PUFA products.

According to animal studies, deficiency of D9D prevents fat accumulation and obesity, provides favorable metabolic effects and seems to reduce obesity-associated white adipose tissue inflammation (6). *In vitro* studies have shown inconsistent results indicating that the effects of D9D on inflammation vary by tissue type (6,7). Low levels of D9D are associated with decreased levels of cardiovascular risk factors like insulin resistance and dyslipidemia in humans (7–10). Additionally, D9D activity is positively associated with the risk of type 2 diabetes,

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Received 3 March 2016; accepted 25 August 2016; advance online publication 19 October 2016. doi:10.1038/pr.2016.186

cardiometabolic diseases (9,11) and with CRP (12,13). D9D expression can be induced by glucose, fructose, SFA, and insulin (7). If the positive association between D9D and CRP observed in adults was based on a causal relationship, it could be hypothesized that changes of dietary patterns may affect CRP levels by modifying D9D activity. This assumption is supported by results of a two-months balanced diet intervention based on nutritional recommendations which decreased both, palmitoleic acid, i.e., the product of estimated D9D activity (calculated as ratio of 16:1n-7 and 16:0), and CRP as well as body weight in metabolically healthy obese adults (14). This may indicate a beneficial effect of reduced D9D activity although no association was observed between FA and D9D with CRP such that other factors like weight loss may have been responsible for the CRP decrease. Palmitoleic acid as an indicator of de novo lipogenesis has been shown to be associated with detrimental metabolic outcomes in several studies (15). In Finnish men, erythrocyte membrane palmitoleic acid was positively associated with CRP (16). In contrast, supplementation of palmitoleic acid for 30 d reduced CRP levels in a randomized controlled trial with 60 adult subjects (17). However, supplementary intake was higher compared with the intake in the usual Western diet (18).

D6D and D5D conversion products, i.e., the LC PUFA arachidonic and eicosapentaenoic acid influence the fluidity and permeability of cell membranes and serve as precursors for prostaglandins and resolvins with effects on inflammation (19,20). In particular, n-3 LC PUFA exert anti-inflammatory effects by several mechanisms such as inhibiting leukocyte chemotaxis, reducing the production of proinflammatory eicosanoids from n-6 PUFA and of inflammatory cytokines as well as by activating antiinflammatory and inhibiting activation of proinflammatory transcription factors (5).

Single nucleotide polymorphisms of the D5D and D6D encoding *FADS* genes were shown to be associated with reduced desaturase activity (21) and increased inflammatory markers (22). In Korean adults, estimated D6D was positively associated with CRP (12,23), whereas D5D was negatively related (23). Additionally, estimated D6D was found to be an independent determinant for plasma levels of CRP (23). Also in a case-cohort study of >1,500 adults including 400 diabetic subjects, estimated D5D was inversely associated with CRP but no association between D6D and CRP was observed (11).

In a recent study based on a sample of 2 to <10 y old children, we found that D9D and D6D to be positively associated with BMI and blood triglycerides; and negatively with HDL z-scores, whereas D5D was negatively associated with BMI and triglycerides in a cross-sectional analysis. When assessing the association between baseline desaturase activities and metabolic outcomes measured 2 y later (follow-up), D9D and D6D were positively associated with the BMI z-score while D6D was inversely associated with HDL (10).

As desaturase activity has been shown to be associated with CRP in adults (12,23), it may also be related to subclinical inflammation in children. Studies investigating the association of desaturase activity and inflammation in children are scarce (24) and completely missing in younger children. Therefore, this explorative study aims to investigate the cross-sectional and longitudinal associations of desaturase activity with high-sensitive CRP in European children aged 2 to <10 y including a high proportion of overweight and obese children.

RESULTS

Table 1 shows the characteristics of the cross-sectional and longitudinal analysis sample. The children included in our study had a high prevalence of overweight/obesity (25) because of the oversampling of overweight and obese children (22.6 and 20.5%, respectively). As expected (26), CRP values were slightly higher in girls than in boys and a higher proportion of children with CRP ≥ Percentile 75 (P75) were obese (68.9% in the cross-sectional population). While D9D and D6D levels were slightly higher with higher CRP values, D5D was slightly lower but only in children in the longitudinal analysis group (**Table 1**). However, in these descriptive data, effects of covariates are not considered.

Table 2 shows the results of the cross-sectional and longitudinal analyses. Each 1 unit increase of D9D (i.e., increase by 0.01 because of the conversion of the scale) was associated with 11% higher odds of having a serum CRP level ≥P75 (odds ratio (99% confidence interval, CI): 1.11 (1.01; 1.22)) whereas D6D and D5D were not associated with CRP. In the longitudinal analysis, no significant associations between CRP and estimated desaturase activities were detected. Adjustment for baseline CRP z-scores did not alter these results.

No interaction between desaturase activity and sex has been found, i.e., the effects of desaturase activity on CRP did not differ significantly between boys and girls. For this reason results are not reported stratified by sex.

DISCUSSION

We analyzed cross-sectional and longitudinal associations between estimated desaturase activities and CRP in a large sample of 2 to <10 y old European children. Our study confirmed a positive association of D9D with CRP as previously observed in elderly men (27) and middle-aged women (11). However, our results do not indicate a longitudinal association between D9D and CRP whereas a high D9D activity seemed to be predictive for elevated CRP in men followed for 20 y (age 50–70 y) (13). One reason for the lack of a longitudinal association in our data might be that D9D (and also CRP) is mainly influenced by the current diet and other factors like the current weight status. Hence, D9D measured at the time of CRP assessment can be expected to have a stronger association than D9D measured 2 y before a CRP measurement. In addition, diet is likely to change rapidly during childhood such that baseline D9D plays a less relevant role as marker of risk of systemic inflammation after 2 y. Examples for nutrients that are known to affect D9D activity by modulating *SCD1* gene expression are SFA, PUFA, and carbohydrates. High intakes of SFA and carbohydrates were shown to increase and dietary PUFA were shown to decrease D9D (7,27). Accordingly, a study with step-wise

Table 1. Characteristics of the cross-sectional and longitudinal analysis group by CRP level[a]

	Cross-sectional population ($N = 1943$)[b]		Longitudinal population ($N = 900$)[c]	
	CRP_T0 < P75[d]	CRP_T0≤P75[d]	CRP_T1 < P75[d]	CRP_T1≥P75[d]
Number of children (%)	1223 (62.9)	720 (37.1)	553 (61.4)	347 (38.6)
Number of boys (%)	619 (63.7)	353 (36.3)	270 (60.8)	174 (39.2)
Number of girls (%)	604 (62.2)	367 (37.8)	283 (62.1)	173 (37.9)
Mean age (SD) at T0, y	6.14 (1.76)	6.55 (1.73)	6.20 (1.71)	6.76 (1.55)
2 to <6 y, *n* (%)	518 (68.2)	241 (31.8)	224 (70.9)	92 (29.1)
6 to <10 y, *n* (%)	705 (59.5)	479 (40.5)	329 (56.3)	255 (43.7)
Weight in categories at T0, *n* (%) ref. (25)				
Thin	93 (79.5)	24 (20.5)	44 (84.6)	8 (15.4)
Normal weight	732 (74.2)	255 (25.8)	348 (77.0)	104 (23.0)
Overweight	274 (62.3)	166 (37.7)	118 (55.9)	93 (44.1)
Obese	124 (31.1)	275 (68.9)	43 (23.2)	142 (76.8)
ISCEDlevel at T0, *n* (%)				
Level 0, 1, 2	189 (57.6)	139 (42.4)	72 (50.7)	70 (49.3)
Level 3, 4	698 (62.5)	419 (37.5)	311 (60.4)	204 (39.6)
Level 5, 6	336 (67.5)	162 (32.5)	170 (70.0)	73 (30.0)
Desaturase activity at T0	Mean (99% CI)	Mean (99% CI)	Mean (99% CI)	Mean (99% CI)
D9D	0.048 (0.047; 0.049)	0.053 (0.052; 0.055)	0.048 (0.046; 0.049)	0.053 (0.050; 0.055)
D6D	0.068 (0.067; 0.070)	0.071 (0.069; 0.072)	0.068 (0.066; 0.070)	0.074 (0.071; 0.076)
D5D	6.215 (6.119; 6.312)	6.231 (6.093; 6.368)	6.310 (6.169; 6.450)	6.061 (5.876; 6.245)
Palmitic acid, 16:0 (%wt)	25.8 (25.7; 25.9)	25.8 (25.7; 26.0)	25.7 (25.5; 25.9)	25.8 (25.6; 26.0)
Palmitoleic acid, 16:1n-7 (%wt)	1.25 (1.22; 1.28)	1.39 (1.34; 1.43)	1.23 (1.19; 1.28)	1.37 (1.30; 1.44)
Linoleic acid, 18:2n-6 (%wt)	18.2 (18.1; 18.4)	18.1 (17.9; 18.3)	18.2 (18.0; 18.4)	18.1 (17.8; 18.4)
Dihomo-γ-linolenic acid, 20:3n-6 (%wt)	1.22 (1.20; 1.23)	1.27 (1.24; 1.29)	1.23 (1.21; 1.26)	1.29 (1.25; 1.33)
Arachidonic acid, 20:4n-6 (%wt)	7.34 (7.25; 7.44)	7.65 (7.51; 7.78)	7.50 (7.37; 7.64)	7.72 (7.52; 7.92)
CRP at T0	Median (75P; 95P)[e]	Median (75P; 95P)[e]	Median (75P; 95P)[f]	Median (75P; 95P)[f]
CRP (mg/l)	0.30 (0.40; 0.80)	1.90 (3.40; 7 .25)	0.30 (0.70; 3.70)	1.10 (2.00; 5.50)
CRP, boys (mg/l)	0.20 (0.40; 0.70)	1.70 (3.20; 7.60)	0.20 (0.60; 2.30)	0.85 (1.90; 6.70)
CRP, girls (mg/l)	0.30 (0.60; 0.90)	2.00 (3.50; 6.90)	0.40 (0.90; 0.45)	1.20 (2.10; 5.10)
CRP z-score	−0.15 (0.19; 0.59)	1.31 (1.75; 2.21)	−0.11 (0.56; 1.75)	0.88 (1.34; 2.12)
CRP at T1				
CRP (mg/l)			0.20 (0.40; 0.70)	1.60 (2.90; 6.70)
CRP, boys (mg/l)			0.20 (0.30; 0.50)	1.60 (2.80; 6.60)
CRP, girls (mg/l)			0.30 (0.50; 0.70)	1.80 (3.00; 6.90)
CRP z-score			−0.05 (0.22; 0.61)	1.34 (1.74; 2.33)

CI, confidence interval; CRP, C-reactive protein; P, percentile; ISCED, International Standard Classification of Education. FA are expressed as weight percentage of all FA detected (%wt).
[a]Groups were categorized according to the 75th percentile of the age- and sex-specific CRP reference values. [b]Cross-sectional population: In 599 of 1943 children (30.8%) CRP values were below or equal to the lower detection limit. [c]Longitudinal population: In 279 of 900 children (31.0%) CRP values were below or equal to the lower detection limit at T0 and in 300 of 900 children (33.3%) this was the case at T1. [d]P75 indicates the 75th percentile of the reference population (26). [e]75P indicates the 75th percentile of the analysis group of our cross-sectional population. [f]75P indicates the 75th percentile of the analysis group of our longitudinal population.

increases of carbohydrate intake confirmed that a high intake promotes an increase of blood palmitoleic acid (15) which could have been caused by increased D9D activity. Thus, dietary changes may have attenuated the relation with CRP. Due to the lack of FA data at follow-up, unfortunately changes in D9D over the 2 y period could not be considered in the present analysis.

Previous studies have shown an association between D9D activity and components of the metabolic syndrome (9,10,23,28) and between increased CRP and the metabolic syndrome (29). If a decrease in D9D activity decreases CRP and thus subclinical inflammation, this may also result in beneficial effects on metabolic syndrome components. On the other hand, reverse causation cannot be ruled out, i.e., it would

Table 2. Odds ratios for having CRP ≥75th age- and sex-specific percentile by 1 unit difference in estimated desaturase activity

	Cross-sectional model[a]		Longitudinal models[b]			
			Effect on T1 CRP, N = 900			
	Effect on T0 CRP, N = 1943		Not adjusted for T0 CRP z-score		Adjusted for T0 CRP z-score	
Desaturase activity at T0	Odds ratio	99% CI	Odds ratio	99% CI	Odds ratio	99% CI
D9D[c]	1.11	1.01; 1.22*	1.05	0.91; 1.21	1.01	0.87; 1.18
D6D[c]	1.02	0.94; 1.11	1.05	0.92; 1.20	1.05	0.91; 1.21
D5D	1.05	0.95; 1.15	0.94	0.81; 1.10	0.93	0.79; 1.09

CI, confidence interval; CRP, C-reactive protein; ISCED, International Standard Classification of Education.
[a]Models were adjusted for age, sex, country, maximum ISCED level of parents, and BMI z-score. [b]The same adjustments were made as under 1 additionally including a binary variable for control vs. intervention regions. [c]For statistical analysis, D9D and D6D were multiplied by 100, i.e., the scale was converted to receive meaningful effect estimates in the models. *statistical significant

also be possible that CRP reduction decreases D9D activity. In adipocytes deficient in the D9D isoform, *SCD1*, expression of the proinflammatory factors monocyte chemoattractant protein 1 (MCP-1) and interleukin (IL)-6 was significantly reduced compared with control adipocytes (30). This would lead to a reduction in CRP produced in response to inflammatory signals, particularly IL-6 (26).

In contrast to our results, D6D was positively and D5D was negatively associated with CRP in boys in a cross-sectional Japanese study with 237 school children aged 11.5 ± 1.5 y. In the same study, no association was seen in girls, which may partly be due to sex hormone effects on D6D and D5D (24). Studies indicate that estrogen seems to stimulate and testosterone seems to inhibit the conversion of the precursor FA to arachidonic and eicosapentaenoic acid (31). However, such effects may be relevant in the Japanese study including school children with a mean age of around 11 y but are improbable in our sample of young and thus mostly prepubertal children. In 489 Japanese adults, serum CRP concentration was inversely associated with D5D in men and women (32).

Our results suggest that low D9D may be beneficial with view to subclinical inflammation If there was a causal relationship between D9D and CRP, dietary modifications such as a decrease of SFA or carbohydrate intake may result in lower D9D and CRP as D9D expression can be induced by these nutrients (7,15), Furthermore, variations in the *SCD1* gene have been shown to influence obesity and metabolic risk factors (33) and may thus affect CRP levels although no such association was seen in a sample of middle-aged adults (34).

In conclusion, our data show that cross-sectionally D9D is positively associated with CRP independent of the weight status in young children. High D9D may indicate an increased risk for subclinical inflammation in young children but may not predict subsequent inflammatory status.

METHODS

In this study, data of a subsample of the IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) cohort were analyzed. In the IDEFICS baseline survey (T0), 16,228 children aged 2 to <10 y from eight European countries were examined in 2007/2008. After 2 y (T1) 11,041 of these children were re-examined. The study design has been described in detail elsewhere (35).

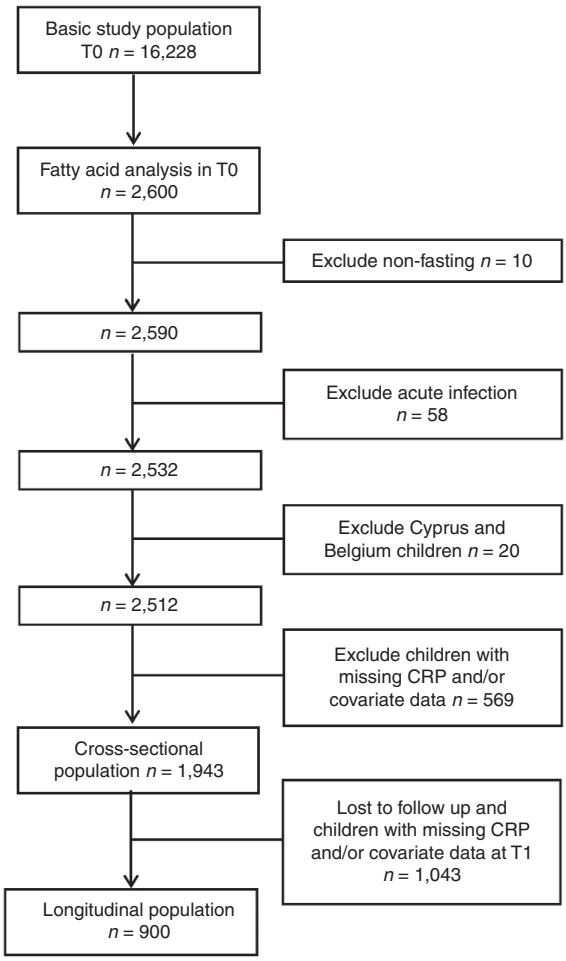

Figure 1. Flow chart of the inclusion and exclusion of IDEFICS participants for the cross-sectional and longitudinal analysis. IDEFICS, Identification and prevention of dietary- and lifestyle-induced health effects in children and infants.

Ethics Statement

The participating centers in each country obtained ethical approval by the competent Institutional Review Boards. For the six countries which provided data for the present analyses these were the following ethics committees: Ethics Committee of the University of Bremen, Bremen, Germany; Tallinn Medical Research Ethics Committee, Tallinn, Estonia; Azienda Sanitaria Locale Avellino Comitato Etico, Avellino, Italy; Regionala Etikprövningsnämnden I Göteborg, Gothenburg, Sweden; Comité Ético de Investigación Clínica de Aragón, Zaragoza, Spain; and Egészségügyi Tudományos Tanács, Pécs, Hungary.

The examination program included standard anthropometric measurements such as body weight and height, a personal interview on health conditions of the child, questionnaires on parental information like educational level and collection of blood samples, as described in detail elsewhere (35).

Fasting blood samples were obtained either by collecting a drop of blood from a fingertip or by venipuncture. A rapid gas-liquid chromatography method was applied to analyze FA composition of whole blood as previously described (36). FA are expressed as weight percentage of all FA detected (%wt). The estimated desaturase activities

were determined from the FA product-precursor-ratios as follows: D9D: 16:1n-7/16:0, D6D: 20:3n-6/18:2n-6, and D5D: 20:4n-6/20:3n-6. D9D and D6D were rescaled, i.e., multiplied by 100 to receive meaningful effect estimates. Body mass index was converted to age- and sex-specific z-scores using the reference values according to Cole and Lobstein (25).

For the assessment of high-sensitivity CRP concentrations in serum latex-enhanced nephelometry (BN2-Nephelometer, Siemens, Eschborn, Germany) was used. The serum CRP values were measured with a precision of 0.1 mg/l and a lower detection limit of 0.2 mg/l.

The FA profiles from T0 fasting blood samples were analyzed in a subsample of 2,600 participants aged 2 to <10 y with oversampling of overweight and obese children. Exclusion criteria were blood drawn in a nonfasting state and acute infections/inflammation defined as CRP level ≥ 10 mg/l (26). As only few children from Cyprus (N = 2) and Belgium (N = 18) provided valid FA data, these two countries were not included in the analysis. **Figure 1** shows selection of the analysis groups for the cross-sectional and longitudinal analyses. The cross-sectional analysis comprises only children with full information on FA, CRP, and covariates (age, sex, country, International Standard Classification of Education (ISCED) level, and BMI z-score) at baseline (N = 1,943). For inclusion in the longitudinal analysis, information on CRP at T1 was required in addition (N = 900 children, due to dropout or missing CRP measurements).

Because of the left-truncated distribution of CRP (due to the large amount of values below the detection limit), CRP values were categorized in being above (≥) vs. below the 75th age- and sex-specific percentile based on recently published reference values (26) for young children. This binary variable was used in the later logistic models. Additionally, age- and sex-specific CRP z-scores were calculated based on the previously mentioned reference values.

As potential confounders, age (continuous), sex, BMI z-score, country and maximum ISCED level of parents were included as covariates. ISCED was aggregated to three categories; low level = 0, 1, 2; medium = 3, 4; high = 5, 6. Additionally, a binary variable indicating control vs. intervention regions was used to adjust for potential differences resulting from an intervention implemented in the study (37).

Logistic regression models were used to assess the cross-sectional associations between T0 CRP (CRP ≥ P75 vs. CRP < P75 (reference)) and the T0 exposures of interest (D9D, D6D or D5D) adjusting for age, sex, BMI z-score, country, and parents' maximum ISCED level. In the longitudinal analyses, again logistic regression models were used to assess the associations between the exposures D9D, D6D, and D5D measured at T0 and CRP category at T1 adjusting for the abovementioned covariates, adding also an indicator for control vs. intervention region. As children with a baseline CRP value close to the 75th percentile may be more likely to exceed the 75th percentile at T1 compared with children with lower baseline CRP, the longitudinal model was in a second step additionally adjusted for the baseline CRP z-scores. All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Cary, NC). To account at least partially for multiple testing we used the 99% CI to determine statistical significance.

STATEMENT OF FINANCIAL SUPPORT

We gratefully acknowledge the financial support of the European Community within the Sixth RDT Framework Programme Contract no. 016181 (Food).

Disclosures and conflict of interest: None.

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