doi: 10.1111/cea.12782

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ORIGINAL ARTICLE **Epidemiology of Allergic Disease**

Higher maternal serum concentrations of nicotinamide and related metabolites in late pregnancy are associated with a lower risk of offspring atopic eczema at age 12 months

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Clinical & Experimental Allergy

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Cite this as: S. El-Heis, S. R. Crozier, S. M. Robinson, N. C. Harvey, C. Cooper, H. M. Inskip, Southampton Women's Survey Study Group and K. M. Godfrey. *Clinical & Experimental Allergy*, 2016 (00) 1–7.

Summary

Background Evidence that atopic eczema partly originates *in utero* is increasing, with some studies linking the risk of developing the condition with aspects of maternal diet during pregnancy. Nicotinamide, a naturally occurring nutrient that is maintained through the dietary intakes of vitamin B3 and tryptophan, has been used in the treatment of some skin conditions including atopic eczema.

Objective To examine the relation of maternal serum concentrations of nicotinamide and related tryptophan metabolites to the risk of atopic eczema in the offspring.

Methods Within the UK Southampton Women Survey, infantile atopic eczema at ages 6 and 12 months was ascertained (modified UK Working Party Criteria for the Definition of Atopic Dermatitis). Maternal serum levels of kynurenine, kynurenic acid, anthranilic acid, tryptophan, nicotinamide and N1-methylnicotinamide were measured in late pregnancy by mass spectrometry (n = 497) and related to the odds ratio of infantile atopic eczema.

Results Maternal nicotinamide and related metabolite concentrations were not associated with offspring atopic eczema at age 6 months. Higher concentrations of nicotinamide and anthranilic acid were, however, associated with a lower risk of eczema at age 12 months (odds ratios 0.69, 95% CI 0.53–0.91/SD change, P = 0.007 and 0.63, 0.48–0.83, P = 0.001, respectively). The associations were robust to adjustment for potentially confounding variables.

Conclusion and clinical relevance This is the first study linking maternal serum concentrations of nicotinamide and related metabolites to the risk of atopic eczema in the offspring. The findings point to potentially modifiable maternal influences on this complex and highly prevalent condition.

Keywords atopic eczema, maternal micronutrients, nicotinamide
Submitted 29 February 2016; revised 7 June 2016; accepted 16 July 2016

Introduction

Atopic eczema is a highly prevalent and complex condition, and evidence that it partly originates *in utero* is increasing. The risk of developing atopic eczema has been linked with a variety of environmental factors in pregnancy, including mother's age, education and smoking, and some studies have proposed links with aspects of maternal diet during pregnancy [1].

Nicotinamide is the amide form of niacin, also known as vitamin B3, an essential vitamin. Both compounds are precursors of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) *in vivo*. Nicotinamide is maintained by the intake of vitamin B3, found in foods including fish, meat, chicken, mushrooms, nuts and coffee, and by the intake of tryptophan, an essential amino acid that is a constituent of most proteins and is the precursor for serotonin and melatonin. In the liver, tryptophan can

be converted to niacin via the kynurenine pathway, with quinolone acids as key intermediates.

The kynurenine pathway (Fig. 1) is the major route for tryptophan metabolism in mammals and is reported to regulate several fundamental biological processes, including cell death. Activation of the tryptophan catabolizing enzyme indoleamine 2,3-dioxygenase, induced by inflammatory stimuli (most importantly interferon-γ), leads to the formation of kynurenine and other metabolites that counter-regulate immune activation; in chronic immune activation, continued immunosuppressive feedback mechanisms lead to elevated kynurenine concentrations. Kynurenine has been reported to enhance IgE-mediated responses [2]. Tryptophan is metabolized through kynureninase and kynurenine transaminase. Kynureninase converts kynurenine to anthranilic acid (AA) and 3-hydroxykynurenine (HK) to 3-hydroxyanthranilic acid (3-HAA). Kynurenine transaminase converts the same two substrates into kynurenic acid (KA) and xanthurenic acid (XA), respectively. 3HAA is further converted to acroleyl aminofumarate, which in turn is converted to quinolinic acid (QA) through non-enzymatic cyclization before conversion to nicotinic acid (niacin), the precursor for NAD. 3HAA and QA can alter Th1 cells [3], thus tending to increase Th2 reactivity. N1-Methylnicotinamide is a metabolite of nicotinamide; produced primarily in the liver, it has anti-inflammatory properties and may also influence thrombosis through activation of prostacyclin activation [4].

In a randomized control trial, topical 2% nicotinamide applied twice a day to atopic eczema for 4 and 8 weeks significantly reduced water loss and increased stratum corneum hydration when compared with white petrolatum [5]. Orally, nicotinamide has been shown to reduce transepidermal water loss [6]. It is not fully understood how oral nicotinamide administration may alter cellular inflammation *in vivo*; in a limited group of healthy human participants exposed to experimental endotoxaemia, it had little effect on cytokines or exhaled nitric oxide [7].

The above observations led us to examine the hypothesis that higher maternal serum concentrations of nicotinamide and related tryptophan metabolites in late pregnancy may be associated with a decreased risk of atopic eczema in the offspring.

Methods

Within the UK Southampton Women's Survey (SWS), a mother–offspring study, information on maternal diet, lifestyle and socio-economic status was collected [8]. Women were followed up through their pregnancies, 3008 delivered a live-born infant with no major congenital growth abnormalities and were assessed for atopic eczema at 6 or 12 months. Of these, 497 had an aliquot available for measurement of serum tryptophan, kynurenine, kynurenic acid, anthranilic acid, nicotinamide and N1-methylnicotinamide concentrations in late pregnancy. Fragmentation confirmed the identity of the analytes. Measurements were made (BEVITAL AS, Norway) using liquid chromatography–mass spectrometry/mass spectrometry [9]; coefficients of variation were < 12%.

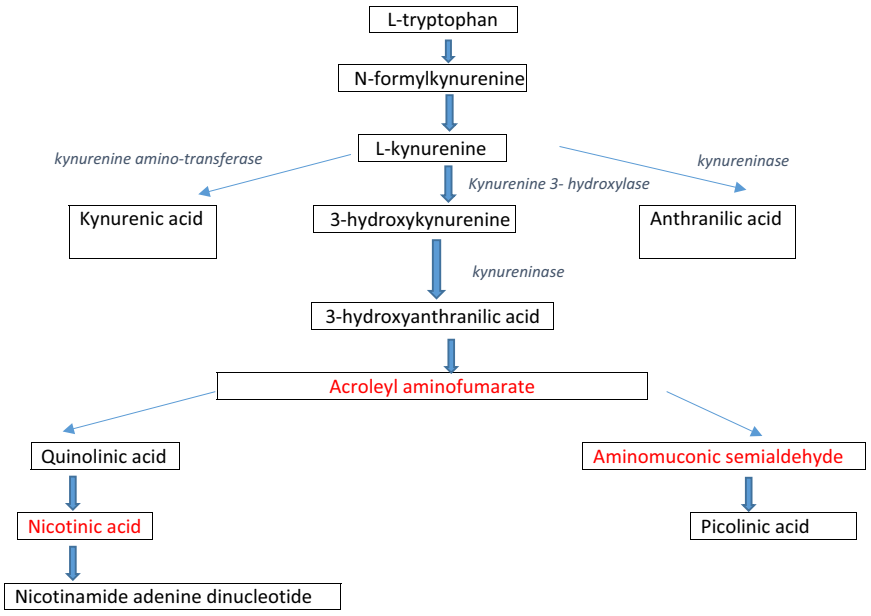

Fig. 1. The kynurenine pathway.

Case definition of atopic eczema was based on the UK Working Party diagnostic criteria for the definition of atopic eczema [10], assessed by trained research nurses who undertook a standardized questionnaire and examination. A personal history of atopy was omitted as a criterion given the young age of the infants, who were not old enough to have developed clearly defined asthma or hayfever.

Metabolite concentrations were transformed using Fisher–Yates transformation [11] to allow analysis of relations per standard deviation (SD) change in concentration. Univariate and multivariate logistic regression analyses were performed (Stata version 13.0, Statacorp LP, TX) to relate maternal demographic and lifestyle characteristics, maternal serum metabolite levels and early life factors to infant eczema at ages 6 and 12 months. Maternal factors that were considered as potential confounders were as follows: age at child's birth, pre-pregnancy BMI, education, smoking, parity and maternal history of eczema increases of elbows or knees in the last 12 months (at 6 months); potential infant confounders were as follows: sex, gestational age, birth weight, breastfeeding duration and filaggrin single nucleotide polymorphism rs7512552 (identified as related to atopic eczema in the SWS cohort as part of the replication studies following a recent multi-ancestry genomewide association study [12], and available for 414 infants in this subsample).

All phases of the Southampton Women's Survey were approved by the Southampton and South West Hampshire Local Research Ethics Committee and parents gave written informed consent.

Table 1. Characteristics of the study population

	n	Median (IQR), Mean (SD) or *n* (%)
Maternal		
Age at child's birth (years)	497	31.2 (3.5)
Pre-pregnancy BMI (kg/m^2)	493	24.2 (22.2–27.2)
A level or higher education	311	62.8%
Smoking in pregnancy	497	62 (12.5%)
Primiparous	243	48.9%
Eczema in the last 12 months	270	9.4%
Duration of gestation at late pregnancy blood sample (weeks)	492	34.5 (0.6)
Maternal serum metabolite concentrations in late pregnancy (n = 497)		
Tryptophan (μmol/L)	497	55.5 (49.1–62.8)
Kynurenine (μmol/L)	497	1.2 (1.1–1.4)
Kynurenic acid (nmol/L)	497	21.9 (17.0–27.6)
Anthranilic acid (nmol/L)	497	14.5 (12.1–16.9)
Nicotinamide (nmol/L)	497	140.2 (81.1–213.6)
N1-Methylnicotinamide (nmol/L)	497	246.2 (164.4–368.1)
Infant		
Male	252	50.7%
Gestational age (weeks)	497	40.1 (39.1–41.0)
Birthweight (kg)	494	3.51 (0.47)
SNP (rs7512552)	414	30.6%
Breastfeeding (completed months)		
Never breastfed	74	15.4%
< 1	95	19.8%
1–3	86	17.9%
4–6	94	19.6%
7–11	86	17.9%
12 or more	45	9.4%
6-month assessment		
Age (weeks)	495	26.7 (25.9–27.6)
Weight (kg)	494	7.99 (0.94)
Atopic eczema as per UK Working Party criteria	53	10.7%
12-month assessment		
Age (weeks)	467	53.6 (52.4–54.6)
Weight (kg)	465	10.12 (1.1)
Atopic eczema as per UK Working Party criteria	64	13.7%

Results

Maternal and infant characteristics are summarized in Table 1. Among the 497 participants, the mother's average age at child's birth was 31.2 years (standard deviation (SD) = 3.5); 48.9% were primiparous and 12.5% smoked during pregnancy. 50.7% of infants were male; mean birthweight of infants was 3.51 kg (SD 0.47) and gestational age 40.1 weeks (IQR 39.1–41.0) and 30.6% of the infants had the rs 7512552 SNP. 10.7% and 13.7% had atopic eczema at ages 6 and 12 months, respectively.

Table S1 shows that the characteristics of the 497 participants in the study group with maternal metabolite measurements in late pregnancy were similar to the overall SWS cohort. However, the study group mothers were older at child's birth, smoking was less prevalent and infants' birthweight was higher.

Table 2 shows univariate analyses of maternal and infant characteristics in relation to infant atopic eczema at age 6 months. Girls had a lower odds ratio of atopic eczema at age 6 months ($P = 0.002$). None of the maternal serum metabolite concentrations were associated with offspring atopic eczema at age 6 months. However, univariate analyses of maternal and infant characteristics showed that higher maternal serum concentrations of nicotinamide and anthranilic acid were associated with lower odds ratios of atopic eczema at age 12 months (Table 3; nicotinamide OR 0.70, 95% CI 0.53–0.90 per SD change, $P = 0.007$, Fig. 2a; anthranilic acid OR 0.63, 95% CI 0.48–0.83 per SD change, $P = 0.001$, Fig. 2b). No significant associations were found with late pregnancy serum levels of tryptophan, kynurenine, kynurenic acid or N1-methylnicotinamide. Higher maternal pre-pregnancy BMI ($P = 0.001$) and male sex ($P = 0.009$) were also associated with higher odds ratios of atopic eczema at age 12 months.

Table 2. Univariate analyses of maternal and infant characteristics as predictors of atopic eczema at age 6 months

	n	OR	95% CI	*P*-value
Maternal characteristics				
Age (years)	495	1.01	0.93–1.10	0.76
Pre-pregnancy BMI (SD)	491	1.29	0.99–1.68	0.06
Education (6 levels)	493	0.99	0.80–1.23	0.95
Smoking in pregnancy (no/yes)	495	0.70	0.27–1.84	0.47
Parity (0/1 +)	495	0.65	0.36–1.15	0.14
Eczema in last 12 months (no/yes)	492	1.98	0.83–4.75	0.13
Maternal serum metabolite concentrations in late pregnancy				
Tryptophan (SD)	495	1.05	0.79–1.40	0.73
Kynurenine (SD)	495	1.04	0.78–1.38	0.80
Kynurenic acid (SD)	495	1.25	0.93–1.67	0.14
Anthranilic acid (SD)	495	0.85	0.63–1.13	0.26
Nicotinamide (SD)	495	0.94	0.71–1.26	0.70
N1-Methylnicotinamide (SD)	495	0.92	0.69–1.23	0.57
Infant characteristics				
Sex (male = 1/female = 2)	495	0.37	0.20–0.69	0.002
Gestational age (weeks)	495	0.99	0.80–1.22	0.93
Birth weight (kg)	492	1.30	0.71–2.36	0.40
Breastfeeding (6 groups)	480	1.02	0.85–1.22	0.86
SNP rs7512552 (no/yes)	413	0.70	0.46–1.09	0.11

SD, standard deviation.

Table 3. Univariate analyses of maternal and infant characteristics as predictors of atopic eczema at age 12 months

	n	OR	95% CI	*P*-value
Maternal characteristics				
Age (years)	467	0.96	0.89–1.03	0.27
Pre-pregnancy BMI (SD)	463	1.49	1.17–1.92	0.001
Education (6 levels)	465	0.85	0.69–1.04	0.12
Smoking (no/yes)	467	1.67	0.83–3.34	0.15
Parity (0/1+)	467	0.71	0.42–1.20	0.20
Eczema in the last 12 months (no/yes)	464	1.28	0.51–3.20	0.60
Maternal serum metabolite concentrations in late pregnancy				
Tryptophan (SD)	467	1.03	0.79–1.34	0.84
Kynurenine (SD)	467	0.90	0.69–1.18	0.47
Kynurenic acid (SD)	467	1.03	0.79–1.35	0.80
Anthranilic acid (SD)	467	0.63	0.48–0.83	0.001
Nicotinamide (SD)	467	0.70	0.53–0.90	0.007
N1-Methylnicotinamide (SD)	467	0.78	0.59–1.01	0.06
Infant characteristics				
Sex (male = 1/female = 2)	467	0.48	0.28–0.84	0.009
Gestational age (weeks)	467	0.95	0.79–1.16	0.64
Birth weight (kg)	464	0.78	0.44–1.37	0.38
Breastfeeding (6 groups)	457	0.92	0.78–1.09	0.36
SNP rs7512552 (no/yes)	387	0.80	0.54–1.18	0.26

SD, Standard deviation.

As concentrations of nicotinamide and anthranilic acid showed a significant correlation ($r = 0.218$, $P < 0.001$), we undertook separate multivariate analyses of each metabolite in relation to atopic eczema, taking account of maternal characteristics and other potential confounding variables (Table 4). Taking account of these other variables, higher maternal serum nicotinamide ($P = 0.013$) and anthranilic acid ($P = 0.003$) concentrations remained significantly associated with lower risks of atopic eczema at age 12 months. The odds ratios and P values changed little after additionally taking account of rs 7512552 SNP, available for a subsample of the group (data not shown).

Discussion

Our results show that maternal nicotinamide and related tryptophan metabolite concentrations were not associated with offspring atopic eczema at 6 months. However, higher late pregnancy maternal concentrations of nicotinamide and anthranilic acid were associated with a lower prevalence of eczema at age 12 months. These associations were resistant to adjustment for potential confounding variables.

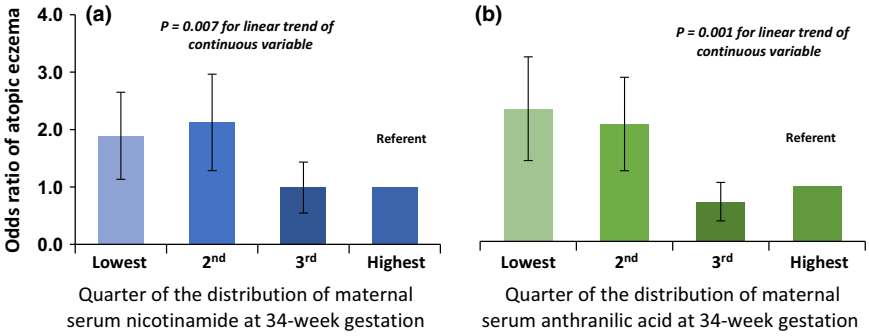

Fig. 2. Atopic eczema at age 12 months in relation to maternal late pregnancy serum concentrations of (a) nicotinamide and (b) anthranilic acid.

Table 4. Multivariate analysis of maternal and infant characteristics as predictors of atopic eczema at age 12 months, including (a) serum nicotinamide, (b) serum anthranilic acid levels in late pregnancy (n = 467)

(a)	OR	CI	*P*-value
Maternal			
Serum nicotinamide (SD)	0.70	0.52–0.93	0.013
Maternal age (years)	1.01	0.93–1.09	0.86
Pre-pregnancy BMI(kg/m^2)	1.07	1.01–1.13	0.02
Maternal education (6 groups)	0.83	0.65–1.06	0.14
Smoking in pregnancy (no/yes)	1.39	0.64–3.04	0.41
Parity (0/1+)	0.62	0.35–1.11	0.14
Eczema (no/yes)	1.28	0.49–3.34	0.62
Infant			
Sex (male = 1/female = 2)	0.48	0.27–0.86	0.014
Gestational age (weeks)	0.97	0.79–1.19	0.74
Breastfeeding duration (6 groups)	0.99	0.81–1.22	0.95
(b)			
Maternal			
Serum anthranilic acid (SD)	0.64	0.48–0.86	0.003
Maternal age (years)	1.00	0.92–1.09	0.98
Pre-pregnancy BMI(kg/m^2)	1.07	1.02–1.14	0.013
Maternal education (6 groups)	0.86	0.68–1.10	0.24
Smoking in pregnancy (no/yes)	1.12	0.51–2.46	0.79
Parity (0/1 +)	0.62	0.35–1.10	0.11
Eczema (no/yes)	1.09	0.41–2.92	0.86
Infant			
Sex (male = 1/female = 2)	0.47	0.26–0.84	0.011
Gestational age (weeks)	0.96	0.78–1.18	0.70
Breastfeeding duration (6 groups)	0.96	0.78–1.17	0.67

Maternal education groups (1 = none, 2 = SCE, 3 = O level (Ordinary Level General Certificate of Education), 4 = A level (General Certificate of Education Advanced Level), 5 = HND (Higher National Diploma), 6 = Degree).

Breastfeeding duration groups (completed months (1 = never tried, 2 = < 1, 3 = 1–3, 4 = 4–6, 5 = 7–11, 6 = 12 or more)).

Nicotinamide is the precursor of NAD and is the sole substrate and an inhibitor of the nuclear enzyme poly-ADP-ribose polymerase 1 (PARP-1) [13]. Through these functions, nicotinamide can enhance energy-dependent cellular processes such as DNA repair [14] and maintain genomic stability and regulation of some transcription factors, particularly in relation to the expression of inflammatory cytokines, chemokines, adhesion molecules and inflammatory mediators [15]. Nicotinamide inhibits cyclic adenosine monophosphate phosphodiesterase (cAMP PDE) and stabilizes mast cells and leucocytes through inhibition of histamine and immunoglobulin E release [16]. It has also been shown to increase the biosynthesis of ceramide and other stratum corneum lipids [17] and prevents the up-regulation of aquaporin, thereby decreasing water permeability and water loss [18]. Nicotinamide can improve the overall structure, moisture and elasticity of skin as it increases the synthesis of collagen and proteins that play an important role in the formation of keratin, filaggrin and involucrin [19]. Through these functions, nicotinamide has the potential to alter the disease processes associated with atopic eczema.

There is only limited evidence of an effect of dietary factors on serum tryptophan metabolite concentrations. Dietary niacin is readily converted to nicotinamide in the body, and challenge studies have shown a robust rise in anthranilic acid concentrations after administration of sodium benzoate, a widely used preservative found in many foods and soft drinks [20]. These observations suggest that influences other than intakes of niacin and tryptophan may underlie the associations we found.

As can be inferred from Fig. 1, lower levels of anthranilic acid and nicotinamide do not point to a specific enzymatic block in the tryptophan pathway either genetically or environmentally induced, and lower levels of these two metabolites may be a general reflection of perturbation of the pathway or low substrate availability. Additionally, our findings (Fig. 2) show a graded association between lower maternal nicotinamide and anthranilic acid levels and the offspring's risk of atopic eczema, pointing away from a simple genetically determined enzymatic block. However, the pathway has not been intensively investigated and we hope our data will stimulate more intensive

investigation including analysis of genetic polymorphisms.

Although total tryptophan is decreased in the third trimester of pregnancy [21], free tryptophan is increased due to decreased binding to albumin, as albumin decreases and non-esterified fatty acids increase in late pregnancy [22]. Nicotinamide is able to cross the human placenta, and fetal blood levels of nicotinamide are greater than corresponding maternal blood levels [23]. There are no reports of adverse effects due to nicotinamide in human fetuses, but the effect of high doses is unknown [23]. There is no human data on maternal use of B vitamins and tryptophan in relation to offspring atopic eczema; however, animal studies on long-term high-dose nicotinamide supplementation in pregnancy have been associated with nicotinamide-induced oxidative tissue injury, insulin resistance and disturbed methyl metabolism that can lead to epigenetic changes [24].

Our study highlights a link between lower maternal nicotinamide levels and related tryptophan metabolites and an increased risk of atopic eczema in the offspring. Strengths of the study are its prospective nature, the standardized assessment of eczema by trained staff and control for confounding factors. Limitations of our study were the relatively small sample size of 497 and the lack of measurements of metabolite levels in early pregnancy. Replicating the findings in other populations would be a valuable next step. Modified UK Working Party Diagnostic Criteria for Atopic Dermatitis were used, in which we omitted atopic disease in a first-degree relative as we are seeking to disentangle the apparent heterogeneous phenotypes that 'atopic eczema' is now thought to represent; excluding those with no family history of atopy would remove an important group of infants from such studies. This modification has, however, not previously been validated. Maternal late pregnancy concentrations of nicotinamide and anthranilic acid were associated with infant eczema at age 12 months but not at age 6 months; this could also reflect heterogeneity in the aetiology and pathogenesis of atopic eczema in early childhood [25]. Although the association was independent of filaggrin status, no information was available on methylation quantitative trait loci that may also influence tryptophan metabolism.

In summary, our study is the first to link maternal serum levels of nicotinamide and related metabolites to the risk of atopic eczema in the offspring. The findings point to potentially modifiable maternal influences on this complex, multifactorial condition and support the evidence that atopic eczema partly originates *in utero*.

Funding

This work was supported by grants from the Medical Research Council, British Heart Foundation, Food Standards Agency, Arthritis Research UK, National Osteoporosis Society, International Osteoporosis Foundation, Cohen Trust, European Union's Seventh Framework (FP7/2007-2013), projects EarlyNutrition and ODIN under grant agreement numbers 289346 and 613977, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, NIHR Musculoskeletal Biomedical Research Unit, University of Oxford and British Lung Foundation.

Author contributions

The authors' responsibilities were as follows – KMG, HMI, SMR and CC were responsible for the design and conduct of the Southampton Women's Survey; SEH and KMG planned the analyses and drafted the manuscript; SEH conducted the statistical analyses with support from SRC; and all authors read and approved the final version of the manuscript.

Conflict of interest

KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone. No other author reports any potential conflict of interests.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Comparison of the study population with the remainder of the SWS participants.