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9 **Residential greenness is differentially associated with childhood allergic rhinitis and aeroallergen**
10 **sensitization in seven birth cohorts**

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92 the article for publication.

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93 **ABSTRACT**

94 *Background:* The prevalence of allergic rhinitis is high but the role of environmental factors remains
95 unclear. We examined cohort-specific and combined associations of residential greenness with allergic
96 rhinitis and aeroallergen sensitization based on individual data from Swedish (BAMSE), Australian
97 (MACS), Dutch (PIAMA), Canadian (CAPPS and SAGE) and German (GINIplus and LISApplus) birth
98 cohorts (N=13,016).

99 *Methods:* Allergic rhinitis (doctor diagnosis/symptoms) and aeroallergen sensitization were assessed in
100 children aged 6-8 years in six cohorts and 10-12 years in five cohorts. Residential greenness was
101 defined as the mean Normalized Difference Vegetation Index (NDVI) in a 500m buffer around the
102 home address at the time of health assessment. Cohort-specific associations per 0.2 unit increase in
103 NDVI were assessed using logistic regression models and combined in a random-effects meta-analysis.

104 *Results:* Greenness in a 500m buffer was positively associated with allergic rhinitis at 6-8 years in
105 BAMSE (odds ratio=1.42, 95% confidence interval [1.13, 1.79]) and GINI/LISA South (1.69 [1.19,
106 2.41]) but inversely associated in GINI/LISA North (0.61 [0.36, 1.01]) and PIAMA (0.67 [0.47, 0.95]).
107 Effect estimates in CAPPS and SAGE were also conflicting but not significant (0.63 [0.32, 1.24] and
108 1.31 [0.81, 2.12], respectively). All meta-analyses were non-significant. Results were similar for
109 aeroallergen sensitization at 6-8 years and both outcomes at 10-12 years. Stratification by NO₂
110 concentrations, population density, an urban versus rural marker and moving did not reveal consistent
111 trends within subgroups.

112 *Conclusion:* Although residential greenness appears to be associated with childhood allergic rhinitis
113 and aeroallergen sensitization, the effect direction varies by location.

Author

114 **INTRODUCTION**

115 Green environments are thought to impart beneficial effects on health by increasing physical activity
116 and stress relief, and by facilitating social interactions. They are also associated with reduced noise, air
117 pollution and heat exposures (1). However, surrounding greenness may play a more complex role on
118 allergic health outcomes. Although a causal relationship remains to be established, studies suggest that
119 children who spend more time in outdoor green environments during early-life may benefit from
120 exposure to a greater number and diversity of beneficial microbes (2,3). A similar protective effect has
121 also been documented between sensitization and a diverse early-life exposure to indoor allergens and
122 microbes (4). However, among those sensitized, exposure to pollen-releasing plants and outdoor fungi
123 may exacerbate allergic symptoms in later childhood (5).

124
125 The few epidemiological studies that have examined associations between residing in/near green places
126 and allergic health outcomes have yielded inconsistent results. Studies report increased (6), no (7),
127 protective (2,8), or conflicting (9) effects, and a recent study concluded that associations appear to
128 depend on the type of greenness evaluated (for example, parks versus forests (10)). These studies differ
129 with respect to their designs, outcomes, populations and green exposure assessment strategies, which
130 may in part explain some of these discrepant findings. For example, the aforementioned studies defined
131 vegetation level using data on tree canopy cover (6), vegetation or land-use types (2,8), the Normalized
132 Difference Vegetation Index (NDVI) (7,9) or several of these measures (10). It is currently unclear
133 which of these exposure metrics may be best. While some more specific measures are able to classify
134 large green areas into land use types (such as the CORINE land use European data), they are not
135 commonly available on a global scale and do not include small green areas. Further, it is possible that
136 different metrics may be more or less relevant to specific pathways. For example, land use data may be
137 very useful for studying physical activity levels, but this is unlikely to represent the main pathway by
138 which greenness might affect allergic diseases.

139
140 As a general measure of vegetation presence, the NDVI index captures vegetation of all sizes using a
141 globally harmonized method, and we chose to use this index to examine cross-sectional associations
142 between residential greenness and allergic rhinitis and aeroallergen sensitization during childhood and
143 early adolescence in seven birth cohorts from Australia, Canada, Germany, the Netherlands and
144 Sweden. As suggestive evidence exists that air pollutants and urbanization may act as confounders or

145 effect modifiers in greenness-health relationships (11,12), we tested interactions between nitrogen
146 dioxide (NO₂) concentrations, population density and a rural/urban indicator with residential
147 greenness, and also adjusted for these factors.

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148 **METHODS**

149 *Data sources*

150 Seven birth cohorts participated: BAMSE (13), CAPPs (14), GINIplus (15), LISApplus (16,17), MACS
151 (18), PIAMA (19) and SAGE (20). Data on several health outcomes, environmental exposures and
152 covariates from all cohorts except MACS had already been harmonized as part of the Traffic, Asthma
153 and Genetics (21) and European Study of Cohorts for Air Pollution Effects (22) collaborations. MACS
154 is here included as this Australian birth cohort adds additional vegetation and geography heterogeneity.
155 Each cohort received ethical approval from their local authorized Institutional Review Boards.

156

157 *Outcome assessment*

158 We focused on health outcomes during childhood (6-8 years) and early adolescence (10-12 years).
159 Information on the cohort-specific study designs and outcome definitions, which varied slightly by
160 cohort, are provided in the Supplemental Information, Table S1. Allergic rhinitis was defined based on
161 a diagnosis during a physician assessment at a follow-up visit in CAPPs and SAGE, parental report of
162 a doctor's diagnosis in GINIplus and LISApplus, parental symptom report in PIAMA and BAMSE and
163 parental symptom or treatment report in MACS.

164

165 Sensitization was assessed by skin prick testing for CAPPs, MACS and SAGE, with a positive reaction
166 defined as having a wheal diameter of ≥ 3 mm. For all other cohorts, sensitization was assessed by
167 measuring allergen specific IgE levels, with a positive reaction defined as any value ≥ 0.35 kU/L, the
168 lower detection limit of the assay. Birch, *Dactylis*, mugwort, ragweed, rye, timothy grass, trees and
169 weeds were considered as outdoor aeroallergens. *Alternaria alternata*, cats, *Cladosporium herbarum*,
170 cockroaches, dogs, feathers, house dust mites and molds were considered as indoor aeroallergens. All
171 available aeroallergens were included in the sensitization analyses. Not all cohorts had information on
172 all aeroallergens or health data at both time points (Supplemental Information, Table S1).

173

174 *Greenness assessment*

175 The NDVI, a green biomass density indicator, was used as a surrogate for surrounding greenness. Its
176 calculation is based on the difference of surface reflectance in visible (0.4–0.7 μ m) and near-infrared
177 (0.7–1.1 μ m) wavelengths. Values range from negative one (water) through zero (rock, sand, snow) to
178 positive one (dense green vegetation) (23). The assignment of NDVI to the home addresses of all

179 cohort participants was done using a harmonized method previously described (24). First, to achieve
180 maximum exposure contrasts, cloud-free satellite images corresponding as close as possible to the
181 spring and summer months during the year of birth of the participants were centrally selected for all
182 cohorts and used to calculate NDVI maps. Negative NDVI pixels were set to zero (replication of
183 analyses with negative NDVI values left as is or set to missing yielded the same results). Second, these
184 images were used to calculate mean greenness in 500m and 1000m circular buffers around the home
185 addresses of participants at 6-8 and 10-12 years of age in order to assess current greenness exposure
186 effects. The 500m buffer was *a priori* selected as the main buffer as it is a proximal measure of a child's
187 neighborhood, may be less prone to exposure misclassification and has been used in previous studies
188 on children (e.g. (25,26)). The 1000m buffer captures a larger area around an individual's neighborhood
189 and was used as a sensitivity analysis.

190

191 The NDVI values used in all main analyses were derived from satellite maps taken at the time of birth
192 of the participants and assigned to their 6-8 and 10-12 year addresses under the assumption that the
193 spatial distribution of greenness would remain stable between these time points. To test this
194 assumption, a second set of NDVI values was created based on satellite maps selected approximately a
195 decade after the birth of the participants and assigned to these same 6-8 and 10-12 year addresses. All
196 main analyses were replicated with this second set of NDVI values. Details of the months and years
197 used for the NDVI assignments for each cohort are provided in the Supplemental Information, Table
198 S1.

199

200 *Statistical analysis*

201 Cohort-specific associations were analyzed using logistic regression. Odds ratios are reported per 0.2
202 unit increase in NDVI (approximately two times the standard deviation in the total population) with
203 corresponding 95% confidence intervals. The GINIplus and LISApplus cohorts were pooled as the study
204 designs are nearly identical and associations are presented per geographical area instead (the rural
205 GINI/LISA North area and GINI/LISA South, which covers the urban city of Munich and its
206 surroundings). Random-effects meta-analysis was used to calculate combined estimates to allow for
207 potential within-and between-cohort heterogeneity (27). The I^2 statistic was used to examine statistical
208 heterogeneity among cohort-specific effect estimates and can be interpreted as the percentage of the
209 variability in effect sizes attributable to the between-study variability rather than sampling error (28). I^2

210 values between 50-90% and 75%-100% represent substantial and considerable heterogeneity,
211 respectively (29). Cochran's Q test was used to test for significant heterogeneity. Analyses for CAPPs,
212 GINI/LISA North, GINI/LISA South, PIAMA, SAGE and the combined meta-analyses (using package
213 "meta" (30)) were conducted centrally using the statistical program R, version 3.1.1 (31). Analyses for
214 BAMSE and MACS were done locally using STATA, version 13 and 13.1 (32), respectively, following
215 the same analysis plan.

216

217 Minimally adjusted models were adjusted for sex and age. Main models were additionally adjusted for
218 parental atopy (not included for MACS as 97% of participants had a history of parental atopy), older
219 siblings, maternal smoking during pregnancy, secondhand smoke exposure concomitant with the time
220 of health outcome assessment (not available for MACS), socioeconomic status (defined as the highest
221 education attained by either parent for BASME, GINI/LISA North, GINI/LISA South, MACS and
222 PIAMA, and maternal age at birth for CAPPs and SAGE), group (intervention for CAPPs, GINI/LISA
223 North, GINI/LISA South, PIAMA and MACS), region (CAPPs and PIAMA only) and cohort
224 (GINI/LISA North and GINI/LISA South only). The influence of additional adjustments for birth
225 weight and exposure to furry pets and mold/dampness in the home at the time of health outcome
226 assessment was examined in sensitivity analyses (MACS not included as these data were generally not
227 available). Covariates were defined as similarly as possible across cohorts using questionnaire-derived
228 information and their selection is based on previous combined analyses of these cohorts with regard to
229 allergic rhinitis and sensitization (9,22,33).

230

231 *Effect modification*

232 To assess effect modification by sex, regression analyses were run including an interaction term
233 between NDVI and sex. In a separate analysis, regression analyses were also run separately for males
234 and females. Effect modification by cohort-specific tertiles of NO₂ concentrations and population
235 density in a 1000m buffer around the home address was also assessed, and models were run stratified
236 by whether participants lived in urban or rural surroundings (data sources and methodology described
237 in the Supplemental Information, page 3). Models were also stratified by whether a child had moved
238 between 1) birth and 6-8 years when considering the childhood health outcomes and between 2) birth
239 and 10-12 years when considering the adolescent health outcomes (CAPPs and SAGE not included as
240 data on moving behavior were unavailable).

241 **RESULTS**

242 *Study population*

243 In total, 13016 children had available information on NDVI exposure and at least one outcome of
244 interest at one time point. The included cohorts varied in size from 3339 children in PIAMA to 327
245 children in MACS (Table 1). Of those with available data, 9.8% (1182/12007) had allergic rhinitis and
246 30.3% (2246/7408) were sensitized to at least one aeroallergen at the age of 6-8 years (13.6%
247 (1346/9885) and 42.1% (1650/3922) are the respective values for 10-12 years). Allergic rhinitis
248 prevalence was lowest in GINI/LISA North and highest among cohorts recruited on the basis of family
249 history (MACS and CAPPS) and SAGE.

250

251 *Distribution of NDVI values*

252 The mean and range of NDVI values in a 500m buffer were similar across cohorts (Figure 1). NDVI
253 estimates in a 500m buffer were highly correlated with those in a 1000m buffer (Pearson's $r > 0.88$).
254 NDVI estimates in the 500m buffer assessed to the childhood and early adolescence addresses were
255 weak to moderately correlated across cohorts for those who moved between these two time points
256 (range of $r = 0.26$ in PIAMA to $r = 0.55$ in BAMSE). NDVI estimates derived using satellite maps
257 obtained for the year of birth and approximately 10 years later ($r > 0.73$) were highly correlated. As it
258 was not possible to obtain cloud-free images for the same months for all cohorts and given that months
259 have different meanings in the different cohorts (for example, when contrasting European and
260 Australian seasons), comparing NDVI distributions across cohorts is not appropriate. Cohort locations
261 and the distribution of NDVI values per cohort are depicted in the Supplemental Information, Figure
262 S1.

263

264

265 *Associations between health outcomes and NDVI*

266 The adjusted cohort-specific associations per 0.2 increase in NDVI for the main models are presented
267 in Figures 2 and 3 for outcomes assessed during childhood (6-8 years) and early adolescence (10-12
268 years), respectively (results per cohort-specific interquartile range increase in NDVI presented in the
269 Supplemental Information, Figure S2). The minimally adjusted models (for age and sex only) were
270 similar (not shown). Greenness in a 500m buffer was positively associated with allergic rhinitis at 6-8
271 years in BAMSE (1.42 [1.13, 1.79]) and GINI/LISA South (1.69, [1.19, 2.41]) but inversely associated

272 in GINI/LISA North (0.61 [0.36, 1.01]) and PIAMA (0.67 [0.47, 0.95]). The effect estimates in the
273 Canadian cohorts were also conflicting but not significant (0.63 [0.32, 1.24] and 1.31 [0.81, 2.12] for
274 CAPPS and SAGE, respectively). The pattern of associations within each cohort for aeroallergen
275 sensitization was similar to those with allergic rhinitis. The pattern also did not differ when
276 associations were stratified into categories of indoor and outdoor allergens, with the exception of
277 SAGE for which the direction of effect estimates varied across outcomes. This suggests that the
278 observed associations with aeroallergen sensitization are not attributable to a single allergen.

279

280 Similar results were obtained for both health outcomes at 10-12 years for the four cohorts with
281 available data at both time points. Associations in the seventh cohort MACS, for which health data
282 were only available at this latter age, were non-significant for allergic rhinitis (0.96 [0.59, 1.57]) and
283 inverse for aeroallergen sensitization (0.57 [0.34, 0.96]).

284

285 Effect estimates were consistent when NDVI was assessed in a 1000m buffer and when models were
286 further adjusted for birth weight and exposure to furry pets and mold/dampness at the time of health
287 outcome assessment (not shown). There was no good indication of non-linearity between NDVI
288 exposures and the health outcomes when associations were examined using generalized additive
289 models, suggesting that at least for these outcomes, a threshold value for NDVI was not apparent.

290

291 Given the substantial/considerable heterogeneity between the cohort-specific associations ($I^2 > 0.7$ for
292 seven of the eight adjusted associations), all meta-analytic results were non-significant (Supplemental
293 Information, Table S2).

294

295 *Effect modification*

296 Although at least one interaction term between NDVI in a 500m buffer and each potential effect
297 modifier considered was significant for at least one cohort, results were not consistent across cohorts
298 and all interaction terms in the combined analyses were non-significant (Supplemental Information,
299 Table S3). In line with this, associations stratified by sex (Supplemental Information, Figure S3) as well
300 as NO₂ (Supplemental Information, Figure S4) and population density (Supplemental Information,
301 Figure S5) tertiles did not reveal consistent patterns within or between cohorts. Stratification by
302 whether participants' lived in urban or rural surroundings yielded weak evidence for stronger positive

303 effects in urban settings in the cohorts for which greenness was positively associated with the health
304 outcomes (BAMSE and GINI/LISA South; Supplemental Information, Figure S6), but confidence
305 intervals overlapped. Independently adjusting the main models for NO₂, population density and urban
306 versus rural categorical variables did not change the results, although the effect estimates for BAMSE
307 were attenuated after adjustment for population density and urban versus rural surroundings (for
308 example, 1.18 [0.81, 1.72] and 1.10 [0.78, 1.54], respectively, compared to 1.42 [1.13, 1.79], for the
309 association between childhood allergic rhinitis and NDVI in a 500m buffer). Finally, models stratified
310 by moving behaviour did not yield consistent differences between groups (Supplemental Information,
311 Figure S7).

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312 **DISCUSSION**

313 Mean NDVI in a 500m buffer was differentially associated with allergic rhinitis and aeroallergen
314 sensitization in this analysis of seven birth cohorts, resulting in an overall non-significant combined
315 finding. Evaluating sex, NO₂ exposure, population density and an urban/rural marker as effect
316 modifiers did not clarify these trends. Confounding by an unknown factor that varies between-study
317 areas or by several region-specific confounders may be a possible explanation. Alternatively, our
318 results may be simply driven by chance.

319

320 It may be worth asking whether a combined meta-analysis is appropriate in this study, given the
321 considerable/substantial heterogeneity observed in the cohort-specific results. We chose to present the
322 meta-analytic results as they answer our original research question. However, the most important lesson
323 from this study may not lie in the direction of the effect estimates but rather upon the use of the NDVI
324 in allergic health research. Although the NDVI is able to capture small-scale greenness in a
325 standardized and objective manner, it does not allow particular types of vegetation to be distinguished,
326 nor are we able to derive individual-level measures of exposure to pollen or other allergenic tree
327 species. The duration and character of potential exposures can also not be assessed. For example, the
328 extent to which NDVI serves as a proxy for exposure to pollen or microbial diversity, or an indicator of
329 areas conducive to physical activity or social interactions, or a proxy for visual impacts related to
330 stress reduction is unclear. We are thus not able to identify which, if any, particular vegetation types,
331 exposure pathway(s) or duration of exposures may drive the observed associations. Consequently,
332 although the use of the NDVI to assess vegetation may be well justified for the evaluation of potential
333 pathways related to stress and for certain health outcomes (for example, birth weight, physical activity
334 and mental health), it appears to be too general of a measure to completely capture the full structure
335 and potential role of the green environment with respect to allergic diseases. We thus caution against its
336 further use in the allergic field and rather recommend that future studies use more detailed data on local
337 tree and herbaceous species and on interactions between people and various measures of vegetation
338 when exploring the role of the residential green environment and the overall living environment on
339 allergic health outcomes. Such measures naturally are more focused on pathways related to pollen
340 dispersion and microbial diversity.

341

342 The current study nevertheless has several strengths. It is the largest analysis of residential greenness

343 on childhood allergic health outcomes to date and the first to include individual-level data from more
344 than one continent. The majority of the health and covariate data had been previously harmonized for
345 these cohorts (21,22), although the allergic rhinitis definitions differed slightly as did the number of
346 objectively measured aeroallergens tested. Also, two cohorts were high allergy-risk by design (MACS
347 and SAGE). These factors could have affected the cohort-specific outcome prevalences, but not
348 necessarily the associations. The high outcome prevalences for some of the cohorts may also have
349 resulted in odd ratios that overestimate the true relative risks, although the overall conclusions of this
350 study would not be affected (34). Several covariates were adjusted for in this analysis, but residual
351 confounding is always possible in observational studies. For example, although models were adjusted
352 for a marker of individual-level socioeconomic status and consistent evidence of effect modification by
353 this factor was not detected (not shown), our measures of individual-level socioeconomic status may
354 not be optimal. It is also possible that area-level factors may play a role.

355
356 Data were prospectively collected for all cohorts except SAGE. Thus, we anticipate that recall bias
357 should be minimal, but remains possible, as does selection bias due to loss of follow-up. Given the
358 cross-sectional design of the analyses, bias related to moving or the effect of timing of exposures
359 (current versus early) was not directly assessed. Findings from a previous study indicate that the green
360 environment around the home at birth may be more strongly associated with allergies later in life than
361 the current home green environment for children that have moved (8). In our study, models stratified by
362 whether a child had moved between birth and the time of outcome assessment did not yield consistent
363 trends. Further, it is unlikely that any bias related to the length of residence at the current address would
364 differentially affect the results across cohorts.

365
366 The harmonized greenness assignment across studies is also an important strength of this study, but is
367 not without limitations. First, it was not possible to obtain cloud-free images for the same months and
368 years for all cohorts. NDVI estimates were derived from images as close in time as possible during
369 spring and summer months to achieve maximum exposure contrasts between areas of low and high
370 greenness. Second, we related NDVI values derived from maps taken at the time of birth to health
371 outcomes 6-12 years later assuming that the spatial variability in greenness exposures would not have
372 changed during this time, an approach often used in air pollution research (22). This assumption is
373 supported by the fact that a second set of NDVI values derived from satellite images taken ten years

374 after the birth of the participants were highly correlated with the main NDVI estimates and yielded no
375 differences in the results. This finding suggests that the spatial distribution of residential greenness was
376 temporally stable during the time frame covered in this study (early/mid 1990s to middle/late 2000s) in
377 the areas investigated. Further studies are needed to confirm whether this finding is also valid in other
378 parts of the world, particularly in developing countries where land use patterns might change more
379 rapidly. Third, our decision to assess associations with greenness in 500m and 1000m buffers around
380 the home address did not allow the study of the effect of greenness on a very small (in a 100m buffer)
381 or large scale (for example, 3000m buffer or even at the city-level). The 500m buffer around the home
382 address was *a priori* selected as the main buffer of interest as it is a proximal measure of a child's
383 neighbourhood and is likely to incorporate less exposure misclassification than larger buffers, although
384 it is well-known that pollen can travel much larger distances (35). The optimal buffer size to use when
385 studying similar associations remains to be determined. Fourth, we chose to limit our analysis to
386 vegetation levels around the home address and did not assess associations with types of green space or
387 land use classifications (e.g. presence or percentage of parks, forest and agriculture) as standard data of
388 this type (e.g. the CORINE data) were only available for the European cohorts and, like the NDVI, do
389 not provide information on vegetation types.

390

391 Although the evidence supporting a beneficial effect of greenness on several health measures is
392 increasing, studies on allergic health outcomes remain inconsistent. In this harmonized analysis of
393 seven birth cohorts from three continents, the direction of the association between mean NDVI in a
394 500m buffer and allergic rhinitis and aeroallergen sensitization varied by region, resulting in a non-
395 significant combined finding. Our results thus suggest that using the NDVI as a marker for residential
396 greenness may only have local interpretations. Alternatively, it is possible that there is no real
397 association between residential greenness and allergic health, and that the observed effects are driven
398 by chance or unknown confounding (region-specific) factors.

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402 MACS, PIAMA and SAGE investigators.

403

404 **CONFLICT OF INTEREST STATEMENT**

405 All co-authors have no conflicts of interest.

406

407 **AUTHOR CONTRIBUTIONS**

408 EF, IM and JH designed the study. EF wrote the initial draft and had final responsibility for the decision
409 to submit for publication. EF, GB and OG conducted the statistical analyses. IM, GB, MK, UG, DS,
410 MB and CC contributed to the greenness exposure assignment. ABecker, DB, AvB, ABergström, BB,
411 IB, MC-Y, SCD, UG, BH, CK, GHK, AK, IK, CL, AL, EM, GP, MS and AW contributed to the
412 collection and/or provided the health and covariate data. All authors provided substantial contributions
413 to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the
414 work, revised the manuscript for important intellectual content, approved the final version and agreed
415 to be accountable for all aspects of the work.

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Table 1: Summary statistics of the study population

	BAMSE		CAPPS		GINI/LISA		GINI/LISA		MACS		PIAMA		SAGE	
	N _{total} =3304		N _{total} =357		North		South		N _{total} =327		N _{total} =3339		N _{total} =682	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Outcomes														
Childhood (6-8 yrs)														
Allergic rhinitis	422	13.4	105	29.4	96	4.8	174	6.3	-	-	211	6.6	174	33.2
Aeroallergen sensitization	623	28.5	154	44.8	256	26.1	481	31.1	-	-	543	32.5	189	27.9
Indoor aeroallergen sensitization	413	20.9	126	36.6	174	17.8	276	17.9	-	-	432	25.8	127	18.7
Outdoor aeroallergen sensitization	503	24.3	73	21.3	183	18.7	338	21.9	-	-	305	18.3	125	18.4
Early adolescence (10-12 yrs)														
Allergic rhinitis	587	19.2	-	-	132	8.0	249	10.9	118	37.0	260	10.1	-	-
Aeroallergen sensitization	-	-	-	-	300	34.8	626	43.0	180	55.1	544	42.6	-	-
Indoor aeroallergen sensitization	-	-	-	-	211	24.5	407	28.0	166	50.8	437	34.2	-	-
Outdoor aeroallergen sensitization	-	-	-	-	223	25.9	478	32.8	116	35.5	356	27.9	-	-
Covariates														
Age at childhood ¹	8.2	(0.5)	7.2	(0.2)	6.1	(0.3)	6.0	(0.1)	-	-	8.1	(0.2)	9.1	(0.5)
Age at early adolescence ¹	13.0	(0.8)	-	-	10.1	(0.2)	10.1	(0.2)	11.2	(2.1)	11.4	(0.3)	-	-
Male sex	1668	50.5	194	54.3	1094	50.8	1469	51.5	172	52.6	1720	51.5	379	55.6
Birth weight (grams) ¹	3528.7	(557.3)	3482.1	(650.6)	3536.8	(478.4)	3415.1	(433.7)	-	-	3521.3	(540)	3378.9	(636.7)
Parental atopy	1007	30.8	331	92.7	1005	47.0	1875	66.1	309	94.8	1666	49.9	395	58.7
Older siblings	1602	48.5	198	55.5	1174	54.8	1231	43.2	204	62.4	1680	50.3	433	73.3

Maternal smoking during pregnancy		415	12.6	29	8.2	321	15.1	375	13.4	13	4.00	537	16.2	131	20.0
Parental education ²	Low	64	2.0	-	-	272	12.7	144	5.1	83	25.4	400	12.0	-	-
	Med	1410	43.9	-	-	875	40.8	513	18.0	-	-	1210	36.4	-	-
	High	1740	54.1	-	-	999	46.6	2188	76.9	244	74.6	1716	51.6	-	-
Maternal age (years) ¹		30.8	(4.5)	31.9	(5.0)	30.8	(3.8)	32.4	(4.1)	32.2	(4.1)	30.5	(3.8)	28.9	(5.3)
Intervention	Active	-	-	167	46.8	727	33.8	852	29.8	109	33.3	309	9.3	-	-
	Placebo	-	-	-	-	-	-	-	-	-	-	272	8.1	-	-
Childhood (6-8 yrs)															
	Tobacco smoke at home	579	18.6	67	18.8	795	38.4	545	19.8	-	-	494	15.6	182	27.5
	Furry pets at home	828	26.2	34	9.5	583	28.1	673	24.0	-	-	1697	54.5	424	62.9
	Mold/dampness at home	250	7.9	175	49.0	306	15.0	590	21.9	-	-	913	29.0	475	69.9
	NO ₂ concentration ¹ (µg/m ³)	11.9	(5.0)	19.5	(11.3)	23.5	(3.1)	20.1	(5.3)	-	-	22.0	(6.1)	8.1	(2.1)
	Population density ³ (1000m buffer)	9341	(15602)	-	-	1218	(1678)	2829	(3389)	-	-	7359	(8395)	-	-
	Living in an urban surrounding ⁴	1117	33.8	-	-	24	1.1	1452	51.1	-	-	661	20.9	-	-
	Moved since birth	2161	66.7	-	-	713	34.1	1378	48.5	-	-	1611	50.8	-	-
Early adolescence (10-12 yrs)															
	Tobacco smoke at home	435	16.1	-	-	464	27.8	309	13.2	-	-	299	11.6	-	-
	Furry pets at home	709	22.9	-	-	596	36.0	822	35.5	-	-	1541	59.8	-	-
	Mold/dampness at home	261	9.9	-	-	317	19.6	504	22.3	-	-	841	32.6	-	-
	NO ₂ concentration ¹ (µg/m ³)	11.5	(5.6)	-	-	23.7	(3.4)	19.8	(5.2)	242 ⁵	(293) ⁵	21.8	(6.1)	-	-
	Population density ³ (1000m buffer)	8315	(12778)	-	-	1309	(1852)	2673	(3258)	5131	(5488)	7076	(8677)	-	-
	Living in an urban surrounding ⁴	893	27.0	-	-	26	1.2	1333	48.8	-	-	515	19.9	-	-
	Moved since birth	2680	82.3	-	-	811	47.2	1546	64.1	173	53.0	1559	60.2	-	-

420

421 ¹ Mean (standard deviation)

422 ² Defined as the highest education attained by either parent

423 ³ Medium (interquartile range) reported

424 ⁴ Defined as $\geq 25\%$ of sealed soil in a 5000m buffer around the home address for BAMSE, GINI/LISA North, GINI/LISA South and PIAMA. Data only available for
425 the European cohorts.

426 ⁵ Minimum distance to a major road in meters (medium (interquartile range)) reported instead as NO₂ concentration data were not available for MACS

427 - : not available/not applicable

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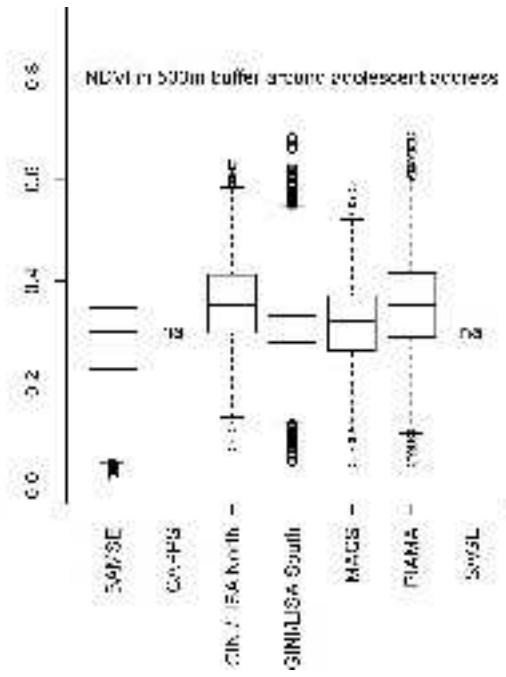
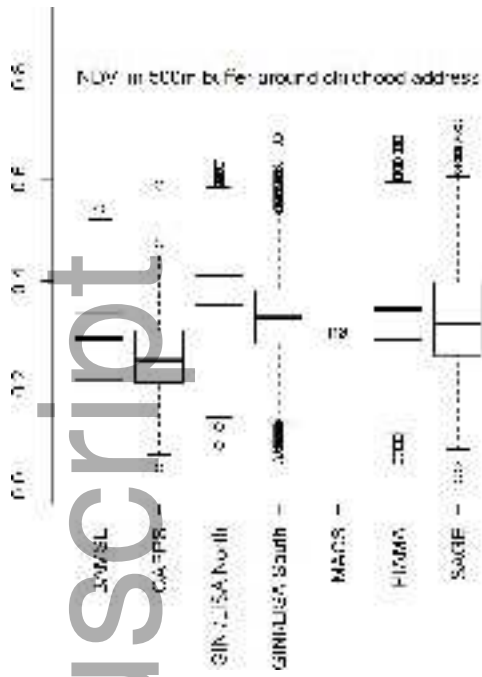
428 **FIGURE LEGENDS:**

429 **Figure 1:** Cohort-specific distribution of mean NDVI in a 500m buffer around the home addresses in
430 childhood (6-8 years) and early adolescence (10-12 years). Comparisons across cohorts are not
431 appropriate as it was not possible to obtain cloud-free images at the same time for all cohorts. na = not
432 available

433 **Figure 2:** Adjusted associations between allergic rhinitis and overall, indoor and outdoor aeroallergen
434 sensitization assessed during childhood (6-8 years) with mean NDVI in a 500m buffer.

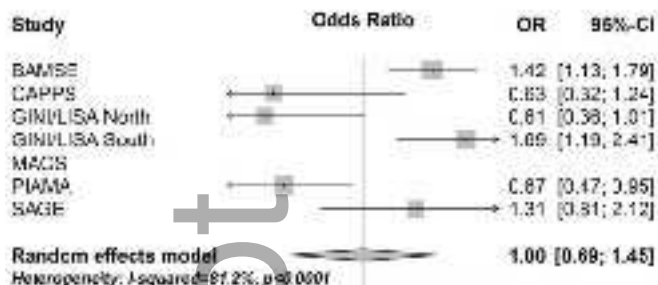
435 **Figure 3:** Adjusted associations between allergic rhinitis and overall, indoor and outdoor aeroallergen
436 aeroallergen sensitization assessed during early adolescence (10-12 years) with mean NDVI in a 500m
437 buffer.

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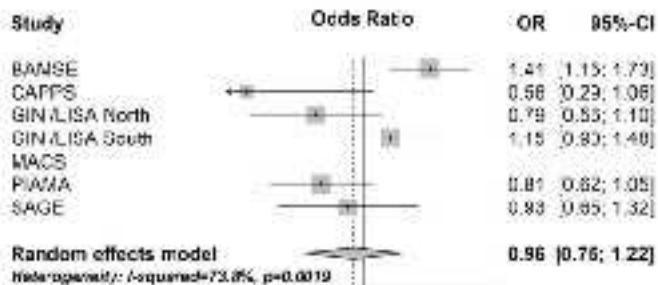


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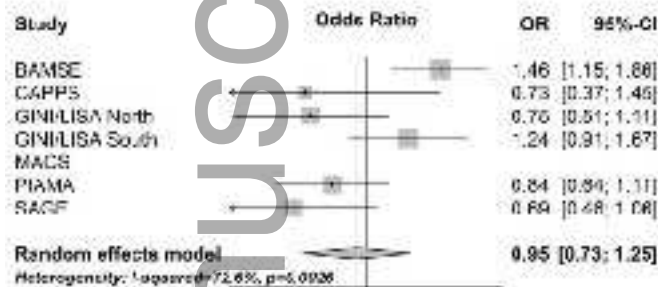
Allergic rhinitis at 6-8 years



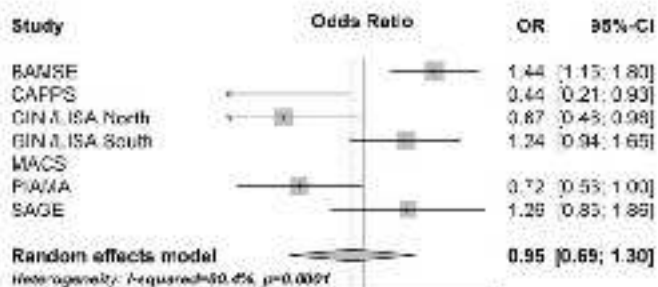
Aeroallergen sensitization at 6-8 years



Indoor aeroallergen sensitization at 6-8 years



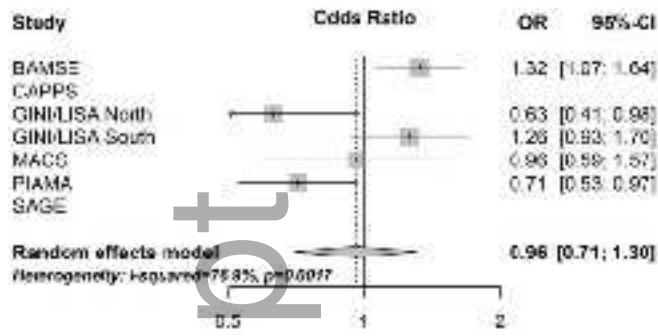
Outdoor aeroallergen sensitization at 6-8 years



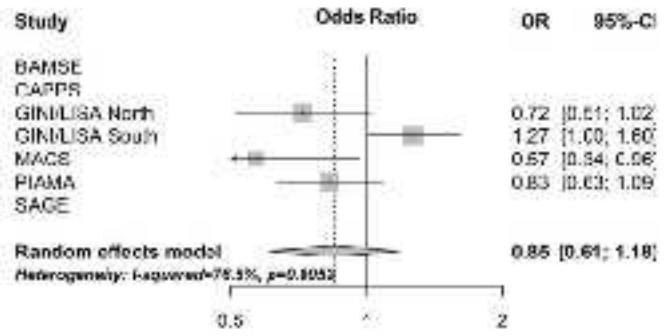
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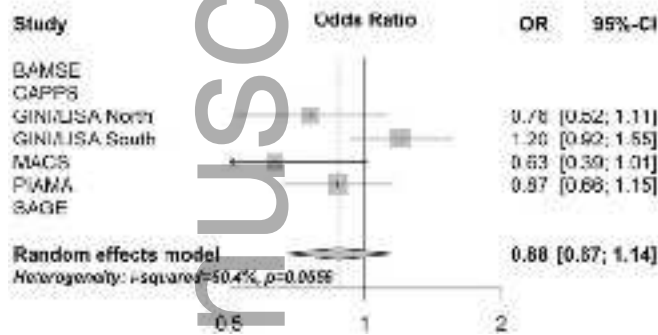
Allergic rhinitis at 10-12 years



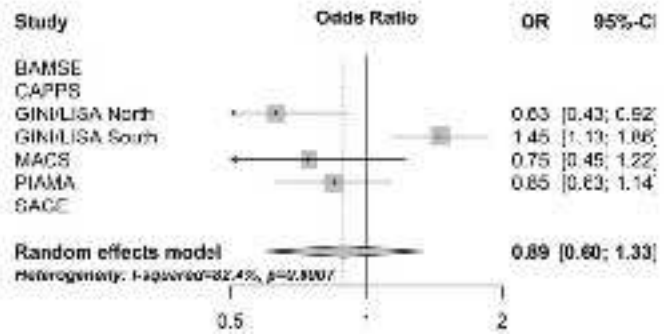
Aeroallergen sensitization at 10-12 years



Indoor aeroallergen sensitization at 10-12 years



Outdoor aeroallergen sensitization at 10-12 years



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