Genome-wide association analysis of 350,000 Caucasians from the UK Biobank identifies novel loci for asthma, hay fever and eczema.

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Abstract

Even though heritability estimates suggest that the risk of asthma, hay fever and eczema is largely due to genetic factors, previous studies have not explained a large part of the genetics behind these diseases. In this GWA study, we include 346,545 Caucasians from the UK Biobank to identify novel loci for asthma, hay fever and eczema. We further investigate if associated lead SNPs have a significantly larger effect for one disease compared to the other diseases, to highlight possible disease specific effects.

We identified 141 loci, of which 41 are novel, to be associated ($P \leq 3x10^{-8}$) with asthma, hay fever or eczema, analysed separately or as disease phenotypes that includes the presence of different combinations of these diseases. The largest number of loci were associated with the combined phenotype (asthma/hay fever/eczema). However, as many as 20 loci had a significantly larger effect on hay fever/eczema-only compared to their effects on asthma, while 26 loci exhibited larger effects on asthma compared with their effects on hay fever/eczema. At four of the novel loci, *TNFRSF8, MYRF, TSPAN8,* and *BHMG1,* the lead SNPs were in LD (> 0.8) with potentially casual missense variants.

Our study shows that a large amount of the genetic contribution is shared between the diseases. Nonetheless, a number of SNPs have a significantly larger effect on one of the phenotypes suggesting that part of the genetic contribution is more phenotype specific. Identified loci and probable causal genes may in the future be used as targets for treatments of asthma, hay fever and eczema.

Introduction

Asthma, hay fever and eczema are common complex immunological diseases affecting many people worldwide (1). The prevalence for these diseases vary among populations and have an underlying architecture that include both environmental and genetic risk factors (1). Comorbidity between asthma, hay fever and eczema is common, and previous genome-wide association (GWA) studies have, apart from identifying a large number of genetic variants associated with risk of disease (2–8) also found evidence of a genetic overlap between the diseases (6, 9).

Family and twin studies have estimated that the contribution of genetic factors, i.e. the heritability for asthma (1, 10, 11) to be 35-95%, for hay fever (1, 11) to be 33-91%, and for eczema (12) to be as high as 90%. A recent large study estimated the SNP-based heritability, the heritability that can be attributed the genetic variation captured by SNPs in a GWA study, to be 15% for asthma, 22% for hay fever, and 9% eczema (6). The same study performed a GWA study that included the first release of UK Biobank (N=138,354) analysing asthma, hay fever and eczema as a combined phenotype and identified 99 significantly associated loci (6). Many of the identified target genes were predicted to influence the function of immune cells, and only six loci were identified to have disease specific effects (6). Many previous GWA studies for asthma, hay fever and eczema have been conducted in different cohorts that were subsequently meta-analysed with the purpose of increasing statistical power (2, 4, 6–8, 13).

The aim with this study was to explain a larger part of the genetic background of self-reported asthma, hay fever, and eczema as well as identify possible novel disease specific effects. We investigated the genetic background of self-reported asthma, hay

70 fever, and eczema combined to a single phenotype, similar as to Ferreira *et al* (6), but
71 in a more homogenous population, as we included both the first and the second
72 release of UK Biobank (N=346,545), compared to Ferreira (6) that only included the
73 first UK Biobank release (N=138,354) as part of a large meta-analysis. We also
74 analysed each disease phenotype independently in larger groups than previous studies
75 conducted in UK Biobank. We further had a larger power to investigated if associated
76 lead SNPs had a significantly larger effect for one disease phenotype compared to the
77 other phenotypes, to highlight possible disease specific effects. Associated SNPs were
78 functionally annotated to assess likely causal mechanisms.
79
80 Although the phenotypes in the UK Biobank are self-reported, the questions are well
81 defined and identical for all participants.
82
83 **Results**
84 Association analysis
85 The UK Biobank includes 502,682 participants, of which 443,068 are Caucasians.
86 The disease prevalence in the Caucasian participants were 11.7% for asthma and
87 23.2% for hay fever and/or eczema (combined). As many as 45.8% of the asthmatic
88 participants had reported having hay fever and/or eczema, and 23.0% of the hay fever
89 and/or eczema participants had reported being diagnosed with asthma (Figure 2). We
90 conducted the GWA study using 346,545 unrelated Caucasians (Table 1), who passed
91 the quality control (QC) for the second UK Biobank genetic data release, and had no
92 ambiguities with regards to disease status. After QC, 15,688,218 genetic variants
93 where included in the analyses (see methods). QC and the final number of included
94 participants in respective analyses are summarized in the methods and in Table 1. We

95 did not identify any statistically significant associations located on the X-
96 chromosome.
97
98 GWA study for self-reported asthma
99 After QC, 41,926 self-reported asthma cases (independent on hay fever/eczema
100 status) and 239,773 controls were included in the GWA analysis. We identified 75
101 risk loci located > 1 Mb apart and containing at least one significantly associated
102 genetic variant ($P \leq 3x10^{-8}$ after adjusting for LD-score intercept of 1.065), that were
103 associated with self-reported asthma, of which 15 loci were found to be novel asthma
104 loci not previously identified in a GWA study (Table 2; Manhattan plot, Figure 1; S1
105 Table and S2 Table; quantile-quantile (QQ) plot, S1 Fig). Using approximate
106 conditional analysis (14), we identified 116 independent significant associations
107 within these 75 loci (S1 Table). The strongest associations for asthma were found
108 within the HLA locus on chromosome 6 ($P=2.06x10^{-100}$), including 14 independent
109 genetic variants. Several genes within this region have previously been reported to be
110 associated with asthma (i.e., *HLA-DQB1, HLA-G* and *HLA-DRB1*) (1, 3, 13). Among
111 the novel asthma loci, some have previously been associated with other similar
112 phenotypes (S1 Table). For example, *SDK1,* previously annotated to the nearby
113 *CARD11* gene, have been reported to be associated with atopic dermatitis (15), but
114 this is the first time that the *SDK1* locus has been identified in a GWA study for
115 asthma. Five of the 15 novel lead SNPs were further replicated in an independent
116 cohort ($P<0.05$; Table 2). However, most of the SNPs were not possible to investigate
117 in the replication cohort, due to a low number of overlapping SNPs between the
118 cohorts.
119
120 *Annotation of asthma associated SNPs*

121 Associated SNPs were further functionally annotated to assess likely causal
122 mechanisms (see Methods). Overlap with GTEx eQTLs were found for 15 of the 75
123 asthma loci. Of these, four eQTLs (*EEFSEC, ADAM19, HHEX* and *TMEM258*)
124 overlapped with the novel loci, where increased expression of *TMEM258* in cell
125 transformed fibroblasts appears to lower the risk for developing asthma (Table 2; S1
126 Table S1 and S3 Table). In contrast, increased expression of *EEFSEC* in lung tissue
127 seems to increase the risk for asthma (S3 Table). Similarly, increased expression of
128 *ADAM19* in whole blood and *HHEX* in cell transformed fibroblasts appears to
129 increase the risk of asthma (S3 Table). 19 probable causal missense variants could be
130 observed within the 75 significant GWA loci of which four missense variants for the
131 15 novel loci (S4 Table). The latter are located within *TNFRSF8, MYRF, TSPAN8,*
132 and *BHMG1*. The association at *TNFRSF8* was represented by only one genetic
133 variant, rs2230624 (S2 Fig). This SNP is a missense variant in two transcripts for
134 *TNFRSF8* and causes a cysteine to a tyrosine substitution which was predicted as
135 'probably damaging' by PolyPhen (16) (PolyPhen-score 0.751-0.921) and had a
136 'deleterious' SIFT-score (17) of 0. The lead SNP at the *MYRF* locus, rs174535, is a
137 missense variant in five transcripts for *MYRF*. Rs174535 causes a serine to arginine
138 substitution and was predicted to be 'probably damaging' by PolyPhen(16)
139 (PolyPhen-score 0.961-1) and had a 'deleterious' SIFT-score (17) of 0.04-0.07.
140 However, rs174535 is also in LD with the most significant eQTL for *TMEM258* in
141 cell transformed fibroblasts. The lead SNP in the *BHMG1* locus, rs11671106, is a
142 missense variant for *BHMG1* and was predicted as 'probably damaging' by PolyPhen
143 (16) (PolyPhen-score 0.94) and had a 'deleterious' SIFT-score (17) of 0.01. The lead
144 SNP at the *TSPAN8* locus, rs11178649, was in complete LD with rs3763978 (R^2=1), a
145 missense variant in three transcripts for *TSPAN8,* which causes a glycine to alanine

146 substitution which was predicted as 'probably damaging' by PolyPhen (16)
147 (PolyPhen-score 0.989) and had a 'deleterious' SIFT-score(17) of 0.03
148
149 GWA study for self-reported hay fever/eczema
150 After QC, 84,034 self-reported hay fever and/or eczema cases that were combined as
151 a single phenotype were included in the analysis. We identified 109 loci to be
152 associated ($P \leq 3x10^{-8}$, LD-score intercept =1.079) with self-reported hay
153 fever/eczema, and 22 of these were novel (Table 3; Manhattan plot, Figure 1; S5
154 Table and S6 Table; QQ-plot, S3 Fig). The strongest association was observed for the
155 lead SNP rs5743604 ($P= 7.5x10^{-72}$) located within *TLR1*. This SNP has previously
156 been associated with allergic disease (6, 21). Using conditional analysis, we identified
157 154 independent significant associations within these 109 loci (Table 3; S5 Table).
158 Moreover, two of our lead SNPs (rs4845604 and rs9986945, mapped to *RORC* and
159 *SDK1*), observed within previously known loci were in low LD ($R^2 \leq 0.05$) with the
160 previously reported genetic variants, indicating that they represent novel variants
161 within or close to known loci (S5 Table). The *UBAC2* locus has previously been
162 reported to be associated with asthma (9), but this is the time that the *UBAC2* locus is
163 reported to be associated with hay fever and/or eczema. We replicated six of the novel
164 lead SNPs in an independent eczema GWA study, the EAGLE consortium ($P \leq 0.05$),
165 (Table 3). However, all SNPs that did not replicate in EAGLE were neither significant
166 in UK Biobank when analysing eczema separately (Table 3).
167
168 *Annotation of hay fever/eczema SNPs*
169 For eleven of the 109 hay fever/eczema associated loci, the lead SNP was in LD with
170 the lead SNP for GTEx eQTLs (Table 3; S3 Table) and 14 overlapped with possible

171 causal missense variants in genes, including *IL6R, IL7R, IL13* and *SMAD4* (S7
172 Table).
173
174 *GWA studies for hay fever and eczema analysed separately*
175 Hay fever and eczema could not be separated for most of the participants, since they
176 had primarily answered yes or no on whether they had either hay fever or eczema.
177 However, to investigate hay fever and eczema individually, we also analysed hay
178 fever (N hay fever cases = 18,915) and eczema (N eczema cases = 7,884) separately
179 in a smaller subset of UK Biobank participants (Manhattan plot, S4 Fig; QQ-plots, S5
180 and S6 Fig). A total of 27 and 18 loci were identified for hay fever and eczema,
181 respectively. One novel hay fever and one novel eczema locus, which has not been
182 reported in previous GWA studies and that were not significantly associated in the
183 combined hay fever/eczema analysis, was detected when analysing hay fever and
184 eczema separately (S8-S11 Tables). The lead SNP, rs12920150 ($P=1.02x10^{-9}$), at the
185 hay fever locus is located close to *CBLN1* and the lead SNP, rs2485363 ($P=1,20x10^{-}$
186 ^{8}), at the eczema locus is located downstream of *TAGAP*. This novel eczema locus
187 was nominally replicated using the summary statistics from the GWA study on
188 eczema in the EAGLE consortium (P=0.018, OR=1.05 [95% CI 1.02-1.92]). Another
189 locus that was not detected when analysing hay fever/eczema combined was detected
190 when analysing eczema separately. The lead SNP for this locus, rs676387
191 ($P=2.26x10^{-10}$), is located within *HSD17B1* (S10 and S11 Tables). This region has
192 previously been reported to be associated with allergic disease (6) and overlap with an
193 eQTL for *TUBG2* in skin, where a decreased expression of *TUBG2* seems to lower
194 the risk for eczema (S3 Table).
195
196 <u>GWA study for asthma/hay fever/eczema (combined as a single phenotype)</u>

197 For the combined analysis of asthma and/or hay fever and/or eczema (N
198 cases=106,752), we identified 110 significant loci (LD-score intercept=1.081), and 16
199 of these were novel GWA loci that have not been significantly associated with either
200 asthma, hay fever or eczema in previous GWA studies (Table 4; Manhattan plot,
201 Figure 1; S12 and S13 Tables; QQ-plot, S7 Fig). However, 12 of these 16 novel loci
202 were detected when analysing asthma and hay fever/eczema separately, while the
203 remaining four novel loci were only found when analysing asthma, hay fever, and/or
204 eczema together as a single phenotype. Using conditional analysis, we identified 164
205 independent associations within these 110 loci (Table 4; S12 Table). The most
206 significant SNP, rs72823641 ($P=1.14x10^{-78}$), was located within *IL1RL1* and was also
207 significantly associated with asthma and hay fever/eczema when these phenotypes
208 were analysed separately ($P = 4.09x10^{-61}$ and $P = 9.64x10^{-64}$) (S12 and S13 Tables).
209 This region has previously been associated with allergic diseases (6) (S14 Table). We
210 also identified five lead SNPs for the combined phenotype asthma and/or hay fever
211 and/or eczema within previously known loci, which were found to be in low LD
212 ($R^2 \leq 0.05$) with previously reported genetic variants, indicating that they represent
213 novel variants within known loci. These five lead SNPs mapped to *LPP, IL31,*
214 *LINC00393, CCR7* and *NFATC* (S12 and S14 Tables).
215
216 *Annotation of Asthma/hay fever/eczema (combined as a single phenotype) SNPs*
217 For 16 of the 110 asthma and/or hay fever and/or eczema associated loci, the lead
218 SNPs overlapped with a lead SNP for an eQTL (Table 4; S3 and S12 Tables). Among
219 the novel loci, one overlapped with an eQTL for *HIST1H2BD* in whole blood
220 ($P=1.11x10^{-16}$). A decreased level of *HIST1H2BD* seems to increase the risk of this
221 combined phenotype (S3 Table). Probable causal missense variants could be observed
222 at 17 out of 110 significant loci and one of these was observed at one of the novel loci

223 located within *TNFRSF8* and was also identified in the asthma analysis above (S15
224 Table).
225
226 SNP-based heritability
227 To quantify the SNP-based heritability for asthma and hay fever/eczema, we used LD
228 score regression analysis (LDSC) (19). These analyses included the same cases and
229 controls as for the association analysis (see Methods). The SNP-based heritability was
230 estimated to be 21% for asthma and 16% for hay fever/eczema (Table 5). Our
231 significant loci, which were located ≥ 1 Mb apart and contained at least one
232 significantly associated genetic variant at $P \leq 3x10^{-8}$, explained 4.2% of the heritability
233 for asthma and 3.6% of the heritability for hay fever/eczema (Table 5).
234
235 Identification of phenotype specific loci (SNP)
236 In our GWA studies, we included all individuals reporting either asthma (for the
237 asthma GWA study) or hay fever/eczema (for the hay fever/eczema GWA study) as
238 cases, independent on if they reported having the other disease phenotype (i.e.,
239 asthma cases could have reported having asthma and hay fever/eczema or only
240 asthma). To investigate possible phenotype-specific SNPs, we performed polytomous
241 (multinomial) logistic regression to identify whether the effect of a locus (lead SNP)
242 was significantly (FDR≤0.05) larger for one disease phenotype as compared to
243 another. These effects can therefore be considered as being disease/phenotype
244 specific. To conduct these analyses, we used four non-overlapping groups: 1) asthma
245 cases without hay fever/eczema (N=22,858), 2) hay fever/eczema cases without
246 asthma (N=65,063), 3) asthma cases with hay fever/eczema (only including N=19,299
247 participants that had reported asthma in combination with hay fever or eczema), and

248 4) controls without asthma, hay fever and eczema (N=240,817) (Figure 2). Hay fever
249 and eczema were not separated in this analysis due to the small sample size (Table 1).
250 Groups were compared in a pairwise fashion (S16 Table).
251
252 A total of 154 lead SNPs (see method section for a description of the selection of lead
253 SNPs), representing the 138 different loci, identified in the GWA study for asthma,
254 hay fever/eczema, or for asthma/hay fever/eczema, were included in polytomous
255 logistic regression analyses. To illustrate the specificity in the Venn diagrams (Figure
256 3), each SNP was assigned to an area that represents either a phenotype-specific effect
257 (significantly larger in one group of cases) or a shared effect (no significant difference
258 between the two groups of cases).
259
260 In the comparison of asthma-only, i.e. without hay fever and eczema, to hay
261 fever/eczema-only, i.e. without asthma, 26 loci/SNPs were specific for asthma-only,
262 i.e. had a significantly higher OR for asthma compared to for hay fever/eczema, while
263 20 loci/SNPs were specific to hay fever/eczema-only. A major part of the loci/SNPs,
264 103, showed no significant difference in effect between these disease phenotypes.
265 (Figure 3; S16 Table).
266
267 When comparing subjects with asthma and hay fever/eczema to subjects with asthma,
268 53 loci/SNPs were specific for asthma with hay fever/eczema. No SNP was specific
269 for the asthma only group (Figure 3; S16 Table). For the remaining 96 loci/SNPs,
270 there was no significant difference in effect between subjects with asthma only and
271 subjects with asthma as well as hay fever/eczema.
272

273 Finally, when comparing cases of hay fever/eczema only with cases of hay
274 fever/eczema combined with asthma (Figure 3; S16 Table), 64 loci/SNPs had
275 significantly larger effect in the group with hay fever/eczema combined with asthma.
276 No locus had a larger effect in the hay fever/eczema without asthma group. As many
277 as 83 loci/SNPs had no detectable difference in effect between these two disease
278 phenotypes.
279
280 For some loci, multiple, possibly independent ($R^2 \leq 0.8$) SNPs were included in the
281 analyses. For most of the analyses, such independent SNPs within the same locus
282 showed the same phenotype specificity, or lack of specificity. That is, all independent
283 SNPs within one locus belong to the same area in the Venn diagram (Figure 3).
284 However, for a number of loci, the effect for the different independent SNPs showed
285 different phenotype specificity. This resulted in 149 independent loci/SNPs when
286 comparing the asthma-only group to the hay fever/eczema-only group and when
287 comparing subjects with asthma and hay fever/eczema to subjects with asthma only
288 (Figure 3). For the last group, when comparing cases of hay fever/eczema only with
289 cases of hay fever/eczema combined with asthma, 147 independent loci/SNPs were
290 identified and included in the Venn diagram (Figure 3). For example, two
291 uncorrelated SNPs ($R^2 < 0.05$) were found to be located within the same intron of
292 *IL2RA:* rs61839660, which was associated with hay fever/eczema, and rs12722547,
293 which was associated with asthma in the GWA study. The rs61839660 SNP has a
294 significantly larger effect in both hay fever/eczema-only and hay fever/eczema with
295 asthma, compared to asthma-only but no difference in effect between hay
296 fever/eczema with or without asthma. The effect of rs12722547 was instead
297 significantly larger in the hay fever/eczema with asthma group, compared to the hay
298 fever/eczema without asthma group. Rs12722547 also exhibited a trend (nominal P =

299 0.05) towards having a larger effect in asthma-only compared to hay fever/eczema-
300 only (S16 Table).
301
302 **Discussion**
303 In this large GWA study, including 346,545 unrelated Caucasian participants from
304 UK Biobank, we identified 141 unique loci that are associated with self-reported
305 asthma, hay fever, and/or eczema when these traits are analysed separately or together
306 as combined phenotypes. In comparison with previous studies based on UK Biobank
307 and similar disease phenotypes, our study has several strengths and presents
308 additional results. Out of all identified loci, as many as 41 are novel to our study and
309 have not been reported to be associated with the same disease phenotype previously.
310 Compared to Ferreira *et al* (6) and Zhu *et al* (9), that only included the first release of
311 UK Biobank, we included the full UK Biobank cohort. We also present five different
312 GWA studies for five different phenotypes and further had the strength to identify a
313 number of possible phenotype specific effects that had not been discussed previously.
314
315 The largest number of loci were associated with combined phenotype (asthma and/or
316 hay fever and/or eczema), most likely due to the larger sample size of this group.
317 However this is in agreement with a shared genetic contribution between diseases, as
318 has been shown in Ferreira *et al* (6) and Zhu *et al* (9). With this combined phenotype
319 (asthma and/or hay fever and/or eczema), we identified four novel loci that were not
320 found for asthma or hay fever/eczema when analysed separately. Three of these loci
321 appear to be highly relevant to the pathogenies of all three diseases: *SMAD7, KLF2*
322 and *RIN3*. The variant at the *KLF2* locus is located in the 5' UTR of *KLF2*. This gene
323 plays a role in processes during development including epithelial integrity,
324 inflammation, and T-cell viability. Previous studies have found associations between

325 this locus and lymphocyte percentage of white cells, neutrophil percentage of white
326 cells, white blood cell counts, monocyte percentage of white cells, and eosinophil
327 percentage of granulocytes (20). The variant at the *SMAD7* locus is located within an
328 intron of *SMAD7.* This gene has previously been associated with inflammatory bowel
329 disease (IBD) (21), colorectal cancer (22), and haemoglobin concentration (20). The
330 variant at the *RIN3* locus, is located within an intron of *RIN3*, and is also associated
331 with *RIN3* expression. This gene has previously been associated with myeloid white
332 cell count, eosinophil basophil counts (20), and chronic obstructive pulmonary
333 disease (23). It is worth noting that some of our novel loci have previously been
334 associated with a related phenotype (S1, S5, S8, S10 and S12 Tables). For example,
335 some of the novel asthma loci has previously been associated with IgE levels,
336 eosinophil counts or dermatitis and some of the novel hay fever/eczema loci with IgE
337 levels or eosinophil counts.
338
339 For four of the novel loci: near *TNFRSF8, MYRF, TSPAN8,* and *BHMG1;* the lead
340 SNP was in LD with potentially deleterious missense variants. The lead genetic
341 variant at the *TNFRSF8* locus, rs2230624, which is associated with asthma as well as
342 the combined asthma/hay fever/eczema phenotype, is a potentially causal missense
343 variant that causes a cysteine to a tyrosine substitution in the TNFRSF8 protein. This
344 protein, which is also referred to as *CD30*, is a receptor that is expressed on activated
345 T and B cells and has been shown in clinical studies to have a role in the development
346 of allergic asthma (24). To the best of our knowledge, this is the first time that this
347 locus has been associated with asthma and allergy in a GWA study. The lead SNP at
348 the *MYRF* asthma locus, rs174535, is a missense variant within the myelin regulatory
349 factor protein (*MYRF*) that causes a serine to arginine substitution near the end of the
350 protein. This gene lies within the fatty acid desaturase (*FADS*) cluster on a fatty acid

351 synthesis-associated haplotype (25). Variants on this haplotype are also strongly
352 associated with expression of *FADS1* and *FADS2,* two genes that are involved in the
353 desaturation of polyunsaturated fatty acids in the biosynthesis of long chain
354 polyunsaturated fatty acids (LC-PUFAs). One of these variants has previously been
355 shown to modulate the effect of breast-feeding on asthma (26); another has been
356 associated with increased risk of inflammation (27). Reduced capacity to desaturase
357 omega-6 LC-PUFAs due to *FADS* polymorphisms has been shown to be nominally
358 associated with reduced risk for development of eczema, potentially due to a
359 pathogenic role of omega-6 LC-PUFAs in development of allergy (28).
360 For seven of the 41 novel GWA loci, the lead SNP was in LD (> 0.8) with an eQTL.
361 We could see a positive correlation between expression of *TUBG2* (in skin), *HHEX*
362 (in cell transformed fibroblasts), *EEFSEC* (in lung and cell transformed
363 fibroblasts), and *ADAM19* (in whole blood) and risk of disease, as well as a negative
364 correlation for *TMEM258* and *HIST1H2BD*. Decreased expression of *TMEM258* in
365 cell transformed fibroblasts was associated with increased risk of asthma.
366 In transgenic experiments in mice, it has been shown that a lower expression
367 of *TMEM258* leads to severe intestinal inflammation (29), which agrees with our
368 results. A possible limitation of this analysis is that it relied solely on the GTEx
369 database. Additional sources of information on eQTLs may increase the total number
370 of eQTLs that are associated with asthma, hay fever and eczema.
371
372 For 16 loci that were associated with asthma, 20 loci associated with hay
373 fever/eczema and for 21 loci associated with asthma/hay fever/eczema, we identified
374 multiple independently associated variants. This indicates that several of the asthma-,
375 hay fever-, and eczema-associated loci represent multiple independent disease-
376 associated variants. As an example, the *FLG* locus contains three independent asthma,

377 and asthma/hay fever/eczema-associated variants. This gene has previously been
378 shown to contain loss-of-function mutations that are causal for skin barrier deficiency
379 and strongly predispose to both eczema and asthma (30). The four most prevalent
380 European *FLG* mutations are c.2282del4, p.R501X, p.R2447X, and p.S3247X (30).
381 An additional example is the *HLA* region whose association with immune diseases is
382 particularly complex and which has previously been suggested to include several
383 independent regulatory factors (31). In our analyses, we identify as many as 21
384 independent associations within this locus.
385
386 As highlighted by this study, as well as previous studies (2–7, 32), many disease-
387 associated loci overlap between asthma, hay fever and eczema. However, several loci
388 were only significantly associated with only one of the investigated phenotypes. By
389 testing for association with hay fever and eczema separately in a smaller set of
390 participants, we were able to resolve some of these signals. Interestingly, one of the
391 strongest associations for hay fever/eczema ($P=7.96x10^{-25}$), found within the *FLG*
392 locus, was more significantly associated with eczema when this phenotype was
393 analysed separately ($P=1.15x10^{-69}$). In contrast, this variant was not associated with
394 hay fever when hay fever was analysed separately. It was, however, associated with
395 asthma ($P=2.37x10^{-27}$). This is in agreement with the previous GWA study by Ferreira
396 *et al*, where a SNP at the *FLG* locus was shown to be specifically associated with
397 eczema (6). However, a different study has shown that mutations within the *FLG*
398 locus are associated with eczema starting in the first year of life, and that these
399 mutations are associated with a later development of both asthma and hay fever (33).
400 This is an example of the typical progression of allergic diseases that often begin
401 early in life, which is commonly referred to as the atopic march (33–35). When
402 analysing hay fever separately, we identified one novel locus near *CBLN1*. Studies on

403 transgenic mice have shown that knock-out of *CBLN1* mimics loss-of-function
404 mutations that occur in the orphan glutamate receptor, *GRID2* (36). Autoantibodies
405 against glutamate receptors are involved in the development of autoimmune disease
406 (37). One novel locus was also identified and replicated when analysing eczema
407 separately, downstream of *TAGAP*. This locus has previously been associated with
408 celiac disease (38) and multiple sclerosis (39).
409
410 We further investigated our novel asthma, hay fever/eczema and eczema loci in two
411 independent cohorts. We were only able to replicate six SNPs out of the 15 identified
412 to be novel for asthma with the summary statistics from the GABRIEL asthma
413 consortium. The GABRIEL GWA study only included 582, 802 SNPs genotyped with
414 the Illumina Human610 quad array, and therefore, a large number of SNPs did not
415 overlap between our studies. However, for most of the loci where we identified the
416 same SNP or a proxy in LD (R2≥0.8), we did find a nominal replication (P≤0.05)
417 (Table 2). The GABRIEL study was based on childhood asthma while the UK
418 Biobank asthma is based on adult asthma and these two disease phenotypes may
419 therefore have some different underlying genetic effects. It is also important to
420 remember that a lack in replication may also be due to a lower power to detect
421 associated SNPs in GABRIEL due to a smaller sample size. Five lead SNPs identified
422 for the combined analysis hay fever/eczema replicated in the EAGLE study (Table 3).
423 The lack of replication is most probably due to differences between phenotypes.
424 While the EAGLE study only included eczema cases, our study also included hay
425 fever. All SNPs that did not replicate in EAGLE, was neither statistically significant
426 when analysing eczema independently in UK Biobank (Table 3). We also tried to
427 replicate the four novel loci that was only identified in the combined analysis,
428 asthma/hay fever/eczema, using the GABRIEL and EAGLE cohorts. However, none

429 were nominally replicated (P‹0.05) which is probably due to the smaller sample sizes
430 in GABRIEL and EAGLE, and most importantly due to the differences in disease
431 phenotypes between the cohort.
432
433 Out of all asthma and/or allergic disease-associated loci that have been reported to the
434 GWAS catalog as of December 2, 2018, the majority (N=108) were nominally
435 replicated in our study (P≤0.05; S14 Table). Twelve associations were not possible to
436 test due to lack of data, i.e. neither the reported SNP nor any SNP in LD with the
437 reported SNP were presented in our data (S14 Table). Asthma, hay fever, and eczema
438 are known to be heterogeneous diseases in which environmental factors play an
439 important role (1). Genetic variants associated with asthma, hay fever and eczema are
440 likely to be population specific (40). It is therefore possible that population-specific
441 variants are not detected in our study. Many of the previous associations that were not
442 replicated in our study have been identified in studies that have used a somewhat
443 different phenotype (41, 42), populations of different ancestry (15, 43) or small
444 sample sizes (< 10,000) (43, 44). Research findings from studies on smaller cohorts
445 are more likely to be false positives, especially when no replication of primary
446 findings has been performed, and are thereby less likely to represent true causative
447 mechanisms (45) (for more information, see S14 Table). A recent GWA study by Zhu
448 *et al* (9), which was also conducted on the UK Biobank cohort, however using a
449 different combination of allergies as a phenotype, reported seven novel allergy-
450 associated loci, five of which were replicated in our study. These loci where not
451 available in the GWAS catalog at the time of writing this article and are therefore not
452 included in S14 Table. The two loci that did not replicate in our study where mapped
453 to *ALG9* on chromosome 11(rs659529) and to *EVI5* on chromosome 1 (rs12743520).
454

455 In previous GWA studies for asthma, the disease phenotype commonly contained
456 other disease phenotypes as well, e.g. participants with asthma commonly also report
457 hay fever/eczema. In contrast, our polytomous logistic regression approach allowed
458 for identification of genetic variants with differing effects between the different sub-
459 phenotypes. These effects can therefore be considered as being disease/phenotype
460 specific. This was achieved by subdividing the participants in four non-overlapping
461 groups depending on asthma and hay fever/eczema status. The SNPs that were
462 included in these analyses were selected from our main GWA analyses, but not
463 including the two SNPs identified for the hay fever and eczema phenotypes analysed
464 separately since we did not have power (large enough sample size) enough to include
465 hay fever and eczema separately in these analyse. This means that a locus that was
466 defined as specific for asthma-only has already been associated with any of the
467 combined phenotypes and/or with asthma, independent of hay fever /eczema status.
468 The association for such variants may have been due to comorbidity between asthma
469 and the other diseases, e.g. a larger fraction of asthma cases in the hay fever/eczema
470 group compared to the controls, or that the effect of the asthma-only specific variants
471 was only partly diluted by being combined with other disease phenotypes. A large
472 number of loci exhibited differential effects between hay fever/eczema-only and
473 asthma-only. As many as 20 loci had a significantly larger effect on hay
474 fever/eczema-only compared to their effects on asthma while 26 loci exhibited larger
475 effects on asthma compared with their effects on hay fever/eczema (Figure 3). Among
476 the loci that were specific for asthma-only, we find *ADAM19* and *ADAMTSL3* which
477 are proteins with multiple biological roles within the cell and believed to be important
478 in a number of diseases, including asthma (46). Among the loci that were specific for
479 hay fever/eczema we find the toll like receptor loci, *TLR1/TLR10*, which also showed
480 a larger effect on hay fever compared to asthma-only in the Ferreira *et al* study (6).

481 Most associated variants at this locus are located within the promoter region of *TLR1*,
482 which encodes the toll-like receptor 1. This protein constitutes a component of the
483 innate immune response to microbial pathogens (47). Several loci that overlap
484 between asthma-only and hay fever/eczema-only were annotated to genes related to
485 tumor necrosis factor (TNF) function, such as *TNFAIP3, TNFAIP8, TNFRSF11A,*
486 *TNFRSF14, TNFRSF6B, TNFRSF8, TNFSF4.* These proteins are mainly expressed in
487 immune cells and regulate immune response and inflammation as well as
488 proliferation, apoptosis and embryogenesis (48).
489
490 The largest number of phenotype-specific loci was observed for the group of cases
491 with asthma and hay fever/eczema (Figure 3; S16 Table), a group of cases that has not
492 been included in similar analyses in previous studies (6). This is a group of
493 participants with an allergic disease in combination with asthma, which could to some
494 degree represent participants with allergic asthma. The number of phenotype-specific
495 loci is considerable larger in our study compared to previous studies that have
496 performed similar analyses, such as the study by Ferreira *et al.*(6),which only
497 identified six disease specific loci. This is not surprising since our analyses included
498 larger sample sizes: N= 65,063, N=22,858, and N=19,299 compared to N= 33,305,
499 N=12,268, and N=6,276 in the study by Ferreira *et al* (6) for the three sub-groups
500 included in the analyses of disease-specific effects. In addition, since only genome-
501 wide significant SNPs were taken forward to the polytomous logistic regression
502 analyses, we used the False Discovery Rate by Benjamini-Hochberg to adjust for
503 multiple testing. This increases the power to pinpoint as many positive findings as
504 possible, still with a small false-discovery rate (5% in our case), compared to the
505 more conservative Bonferroni method used in the previous study by Ferreira *et al* (6) .
506 The previous study, also separated hay fever and eczema, and compared the three

507 groups hay fever-only, eczema-only and asthma-only. Since different subgroups of
508 cases were analysed in our study our results do not disagree with that of Ferreira *et al*
509 (6) that found six disease-specific SNPs: near *FLG, RPTN-HRNR* (close to *FLG*),
510 *IL2RA, IL1RL2- IL8R1, WDR36-CAMK4* and *GSDMB;* where five of them were
511 significantly different between hay fever and eczema.
512
513 The SNP-based heritability was estimated to be 21% for asthma and 16% for hay
514 fever/eczema. These percentages represent the portion of heritability that can be
515 captured by the common genetic variants that were included in the GWA study. The
516 SNP-based heritability for asthma has previously been estimated at 15%, which is
517 slightly lower than the estimate from our study and probably due to a smaller sample
518 size, and/or a difference in disease definition in the previous study (6). In comparison
519 to the high estimates for the heritability (33-95%) from family and twin studies (1, 10,
520 12), this suggests that a major contribution to the genetic risk for asthma, hay fever
521 and eczema might not be identified in studies using common genetic variants, or need
522 cohorts with even larger sample sizes. However, heritability estimates from family
523 and twin studies have been suggested to be overestimated (49–51) due to the fact that
524 these estimates often are based on simplistic models that ignore shared environmental
525 factors. Our estimate might also be lower due to the presence of disease-associated
526 rare variants that are not captured by the SNP-based heritability estimate.
527
528 A possible limitation of the present study is the self-reported phenotypes, which might
529 lead to a recall bias and misclassification. Another limitation is that the UK Biobank
530 cohort traits are not independent since there are shared cases between asthma, hay
531 fever and eczema and completely shared controls. However, findings presented in this
532 article apply to a single large population of individuals of similar age. Population

533 stratification was also controlled for by filtering for Caucasian participants, including
534 ancestry derived principal components and adjusting for the LD-score intercept in our
535 analyses. Participants of the UK Biobank are also more likely to be exposed to more
536 similar environmental factors, compared to the participants of previous meta-analyses
537 that utilise a large number of smaller cohorts from different countries and age-groups.
538 Analysing hay fever and eczema as a combined phenotype is another limitation in our
539 study, which prohibits identification of hay fever- and eczema-specific SNPs. We
540 therefore refer to SNPs as phenotype-, rather than disease-specific in the polytomous
541 logistic regression analyses. However, both hay fever and eczema are IgE mediated
542 hypersensitivities and therefore probably share similar physiology (52).
543
544 **Conclusion**
545 In summary, we describe 15 novel loci for asthma, 22 novel loci for hay fever and/or
546 eczema and an additional four novel loci were found when analysing asthma, hay
547 fever and eczema together. Two novel loci were also identified when analysing hay
548 fever and eczema separately. Pinpointing candidate genes for common diseases are
549 important for tailor-made studies that want to prioritize candidate genes for
550 developing novel therapeutic strategies. This study further highlights a large amount
551 of shared genetic contribution to these diseases, indicating that the comorbidity
552 between asthma, hay fever and eczema is partly due to shared genetic factors.
553 However, we also show that a number of SNPs have a significantly larger effect on
554 one of the phenotypes, suggesting that part of the genetic contribution is phenotype
555 specific.
556
557
558

559 **Methods**

560 Study population

561 The UK Biobank includes 502,682 participants recruited from all across the UK.
562 Participants were between 37 and 73 years old at time of recruitment between 2006 and
563 2010. Most participants visited the centre once, but some individuals visited the centre
564 at up to three times. Participants answered questions about self-reported medical
565 conditions, diet, and lifestyle factors. A total of 820,967 genotyped SNPs and up to 90
566 million imputed variants is available for most participants. The UK Biobank study was
567 approved by the National Research Ethics Committee (REC reference 11/NW/0382).
568 An application for using data from UK Biobank has been approved (application nr:
569 15479). We included 346,545 unrelated Caucasians (see selection of participants and
570 sample QC below) with genotypes from the second UK Biobank genotype release
571 (Table 1).

572

573 Disease phenotypes: asthma and hay fever/eczema

574 Self-reported asthma as well as self-reported hay fever and/or eczema (combined)
575 were assessed using the UK Biobank touch screen question number (Data field 6152),
576 which asked the participants the following question: *has a doctor ever told you that*
577 *you have had any of the following conditions? (You can select more than one*
578 *answer):* 1) asthma and 2) hay fever, allergic rhinitis or eczema, 3) none of the above
579 or 4), prefer not to answer. Because hay fever and eczema diagnosis could not be
580 separated we called this variable hay fever/eczema (i.e., participants reported hay
581 fever and/or eczema). All participants were also invited to participate in an interview.
582 At first, nurses (trained UK Biobank staff-member) confirmed with each participant
583 that the information they provided on the screen or questionnaire was correct if they
584 had answered that a doctor had told them they had one or more of the following

585 diseases: heart attack, angina, stroke, high blood pressure, blood clot in leg, blood clot
586 in lung, emphysema/chronic bronchitis, asthma, or diabetes. Due to the confirmation
587 of asthma cases, the overlap in asthma variables between the touch-screen
588 questionnaire and verbal interview was very high. For asthma, only 622 individuals
589 were removed due to conflicting answers between the touch-screen and verbal
590 interview. Using a drop-down menu, the nurses could also add other diagnoses. These
591 diagnoses (UK Biobank data field 20002) were used to define hay fever and eczema
592 cases separately. However, the disease prevalence in this variable appears to be
593 largely underreported as many individuals reported hay fever or eczema in the touch-
594 screen questionnaire but did not report hay fever or eczema during the interview. For
595 this reason, the touch-screen data variables hay fever/eczema, with a much larger
596 sample size (Table 1) compared to hay fever and eczema separately, was used as one
597 of the primary phenotypes analysed in this study. For hay fever/eczema, 4,881
598 individuals were removed due to conflicting answers between the touch-screen
599 questionnaire and the interview, for individuals reported they had hay fever during the
600 interview but not on the touch-screen questionnaire (N=2,143), or reported they had
601 eczema in the interview but not in the touch-screen (N=2,738). We further removed
602 22 individuals who had asked to be removed from the UK Biobank.
603
604 Controls
605 Controls (N=239,773) were selected as individuals answering "none of the above" in
606 question 6152, and who did not report asthma, hay fever or eczema in variable
607 number 20002. The same controls were used for all phenotypes.
608
609 *Genotyping*

610 The UK Biobank Axiom array had been used to genotype 438,417 of the 502,682 UK
611 Biobank participants. The other 49,994 samples (all from the interim release) had
612 been genotyped on the closely related UK BiLEVE array. The UK BiLEVE cohort
613 and the rest of the UK Biobank differ only in small details of the DNA processing
614 stage. The two arrays have 95% common marker content. We included a variable for
615 array type (UK BiLEVE or UK Biobank Axiom) as covariate. SNPs in UK Biobank
616 were imputed using UK10K (53) and 1000 genomes phase 3 (54) as reference panels.
617 Imputation in the second release resulted in 92,693,895 SNPS (released in June 2017).
618 However, because the UK Biobank reported problems with imputation quality for a
619 subset of the SNPs (caused by mismatch in coordinates between the UK10 and the
620 1000 genomes reference panels), we followed the recommendation to only include
621 genetic variants included on the HRC panel (55) (N=39,727,058).
622
623 Quality control
624 Quality control of genotype data and imputation of genotypes had already been
625 carried out centrally by UK Biobank. From the imputed dataset, we only included
626 SNPs in the HRC panel with a MAF ≥ 0.01. We removed SNPs deviating from
627 Hardy-Weinberg (P-value < $1x10^{-20}$) and markers with more than 5% missing
628 genotype data. We only included SNPs with an imputation quality >0.3. After QC, a
629 total of 15,688,218 autosomal SNPs and SNPs on the X-chromosome were included
630 in our analyses. We only included Caucasian participants who were clustering
631 according to the genetic principal components (56,180 non-Caucasians were
632 removed: individuals listed in UK Biobank data file 22006). We further removed first
633 and second-degree relatives (N=32,751), using kinship data (estimated genetic
634 relationship > 0.044), and participants with sex discordance, high
635 heterozygosity/missingness (individuals listed in UK Biobank data field 22010 and

636 22027), and participants with more than 5% missing genotypes. After QC and
637 exclusion, 346,545 unrelated Caucasian participants remained.
638
639 Genome-wide association study
640 A GWA study were performed for each phenotype using logistic regression and an
641 additive genetic model implemented in PLINK version 1.90 (56). We performed a
642 GWA studies for five sets of phenotypes: 1) asthma (independent on hay fever and
643 eczema status), 2) hay fever/eczema (hay fever and/or eczema independent on asthma
644 status), 3) hay fever and/or eczema and/or asthma, as well as 4) hay fever
645 (independent on asthma and eczema status) and 5) eczema (independent on asthma
646 and hay fever status). The same controls, that have reported that they did not have any
647 of the disease phenotypes, were used for all analyses (N=239,773). The following
648 covariates were included in our analysis: Townsend deprivation index (TDI) (as a
649 proxy for socioeconomic status), sex, age, smoking, and the first ten ancestry derived
650 principal components. In addition, to adjust for the different genotyping chips, we
651 included a binary indicator variable for UK Biobank Axiom versus UK BiLEVE
652 genotyping array. We calculated the LD-score intercept, using the LD score
653 regression software (LDSC) (19), for each phenotype and adjusted the summary
654 statistics accordingly (19). The genome-wide significance threshold was set to $3x10^{-8}$,
655 as suggested for GWA studies that include variants with a minor allele frequency
656 (MAF) ≥ 0.01(57), which was the threshold used in our study. Individual loci were
657 defined as regions with at least one significantly associated SNP ($P \leq 3x10^{-8}$). Start
658 and stop positions for each locus were where no additional significantly associated
659 SNPs could be found (upstream for start position, or downstream for stop position)
660 within 1 Mb.
661

662 Identification of additional independent variants within associated loci

663 To identify independently associated variants within each defined locus (significant
664 SNPs ($P \leq 3x10^{-8}$), within 1 Mb), we used an approximate conditional analyses
665 implemented in GCTA (14). LD calculations were based on 5,000 randomly selected
666 Caucasian participants from UK Biobank (after sample QC). For each locus, the most
667 significant top SNP was identified and the summary statistics of all SNPs within the
668 same locus was adjusted by the effect of the lead SNP. After adjusting for the lead
669 SNP, we identified the most significantly associated SNP within the locus that
670 remained significant ($P \leq 3x10^{-8}$). In the next step, we once again adjusted the
671 summary statistics of all SNPs within the same locus, by including the effect of both
672 the original lead SNP and the conditional lead SNP form the first iteration. This
673 process was thereafter repeated until no other SNPs within the locus were found
674 significant after adjusting for all previously detected independent lead SNPs.

675

676 Determining the novelty status of significant loci

677 To determine whether significant loci were novel to any of the diseases, we compiled
678 a list of all asthma, hay fever, eczema and allergy risk SNPs with genome-wide
679 significant association ($\leq 5x10^{-8}$) reported in the NHGRI-EBI GWAS catalog
680 (downloaded December 2, 2018). We also searched for GWA study results using
681 PubMed and bioRxiv. We classified a locus to be 'novel, if the locus was > 1 Mb
682 from any of the previously reported loci/variants for the disease. We also estimated
683 LD between each lead SNP and all genome-wide significant associations found in the
684 NHGRI-EBI GWAS catalog, to determine whether the lead SNP was a novel variant
685 in a known locus (if the locus was < 1 Mb from any of the previously reported
686 loci/variants for the disease). We considered our associated SNP to be a novel variant

687 if R^2 were smaller than 0.05 between our top associated variant and previously
688 reported variants within the same locus. A locus was also reported as novel for a
689 specific disease (i.e., asthma) if previous GWA studies only reported association to a
690 different allergic disease (for example hay fever). If the locus was previously reported
691 for a combined phenotype, i.e. in studies combining different allergic diseases,
692 including the one tested, it was not reported as a novel locus.
693
694 Annotation of target genes and identification of causal genetic effects
695 To identify likely target genes for associated variants, we first reported the closest
696 gene(s) to the lead SNP for each locus and reported if the SNP was intronic or exonic
697 using the Human Genome Browser (GRCh37). We also performed additional
698 analyses to potentially better define plausible target genes. To examine the
699 relationship between the lead SNP for each locus and gene expression we used the
700 Genotype-Tissue Expression (GTEx) database (58) to find evidence of overlap with
701 expression quantitative loci (eQTLs). We downloaded significant eQTLs from the
702 Genotype-Tissue Expression (GTEx) database. First, we selected GTEx SNPs that
703 overlapped with the UK Biobank SNPs and used a conservative significance threshold
704 $P \leq 2.3 \times 10^{-9}$ for cis effects (<1 Mb) form the GTEx data, in agreement with
705 previous studies (6). Second, we identified the most significant eQTL SNP for each
706 tissue and gene in the GTEx dataset. Third, we estimated the LD between the lead
707 eQTL SNPs and our lead GWA study SNPs. A lead GWA SNP in LD ($R^2 > 0.8$) with
708 a lead GTEx eQTL SNP was considered to overlap with the eQTL. Only cells or
709 tissues that were relevant for our disease phenotypes were considered when searching
710 for eQLTs, including EBV-transformed lymphocyte, transformed fibroblasts, whole
711 blood, lung and skin (sun exposed and not sun exposed).
712

713 We also used the Bioconductor biomaRt (59) package in R for functional annotation
714 of associated SNPs. In BiomaRt, lead SNPs, and all SNPs in LD (R^2>0.8) with a lead
715 SNP, were cross-referenced against: Ensembl Genes, Ensembl Variation, and
716 Ensembl Regulation version 91 (Accessed 9 December 2017 using the human
717 assembly GRCh37). Here we checked whether the lead SNPs were in LD (R^2>0.8)
718 with a potentially functional genetic variant by investigated regulatory features for the
719 SNPs (i.e., promoters, enhancers etc.), binding motifs (i.e., if any of the SNPs were
720 found within a motif for a transcription factor), and if the SNPs were possibly
721 damaging variants (i.e., missense, stop gained, stop lost, or splice acceptor/donor
722 variants) and if the variants were predicted to be deleterious by SIFT or PolyPhen.
723
724 Replication
725 We replicated our novel asthma, hay fever/eczema and eczema loci in two
726 independent cohorts the EAGLE eczema consortium and the GABRIEL asthma
727 consortium (P≤0.05). Our novel loci identified for asthma was replicated using the
728 summary statistics from the GABRIEL consortium which consisted of 10,365
729 physician-diagnosed asthmatic cases and 16,100 healthy controls (60). All individuals
730 in GABRIEL were genotyped for 582,892 SNPs using the Illumina Human610 quad
731 array. More information on this cohort has been published elsewhere (60). The
732 EAGLE consortium GWA summary statistics consists of 21,000 atopic dermatitis
733 (eczema) cases and 96,000 controls (61) and were used to replicate novel loci for hay
734 fever/eczema and eczema analysed separately. Further information about this cohort
735 has been published previously (61). If the lead SNP from our study was not found in
736 GABRIEL or EAGLE, we search for a proxy in LD (≥0.8) with the lead SNP.
737
738 SNP-based heritability

739 To quantify the SNP-based heritability for asthma and for hay fever/eczema
740 (combined as a single phenotype) we used LD score regression software (LDSC) (19)
741 including the same cases and controls as for the association analysis for each
742 phenotype (19). To calculate the heritability on the liability scale, we needed to adjust
743 for disease prevalence. Since this was a population-based study, we set the Caucasian
744 population and sample prevalence to the one calculated for each disease in UK
745 Biobank. We included 1,108,908 HapMap SNPs to calculate the heritability for
746 asthma and hay fever/eczema. We also removed all significant loci from each
747 individual GWA study result to estimate how much of the heritability was explained
748 by the significant loci reported in this study.
749
750 Identification of phenotype-specific loci (SNP)
751 To identify possible phenotype-specific SNPs, we performed polytomous
752 (multinomial) logistic regression to identify whether the effect of a locus (lead SNP)
753 was significantly (FDR≤0.05) larger for one disease phenotype as compared to
754 another. These effects can therefore be considered as being disease/phenotype
755 specific. To conduct these analyses, we used four non-overlapping groups: 1) asthma
756 cases without hay fever/eczema (N=22,858), 2) hay fever/eczema cases without
757 asthma (N=65,063), 3) asthma cases with hay fever/eczema (only including N=19,299
758 participants that had reported asthma in combination with hay fever or eczema), and
759 4) controls without asthma, hay fever and eczema (N=240,817) (Figure 2). Hay fever
760 and eczema were not separated in this analysis due to the small sample size (Table 1).
761
762 We performed polytomous logistic regression for all possibly independent (R^2<=0.8)
763 associated lead SNPs identified in the asthma, hay fever/eczema or asthma/hay
764 fever/eczema GWA studies. For some regions, different SNPs, that represent the same

765 signal (R^2>0.8 between the SNPs), were identified in the different GWA studies. For
766 these regions, only the SNP with the lowest P-value from the original GWA study
767 was included in these analyses. For regions where, different lead SNPs were
768 identified in the different GWA studies, and where these lead SNPs were not in strong
769 LD (R^2<=0.8), all lead SNPs were included in the analyses.
770
771 The polytomous (multinomial) logistic regression was performed with the response
772 variable, *Y,* being categorically distributed with K=4 non-overlapping
773 groups/outcomes (the four non-overlapping groups are explained above). Out of
774 K·(K-1)/2=6 comparisons in total, there are K-1=3 independent comparisons. The
775 logit function is defined as the logarithm of the quotient between the probability of a
776 given outcome (e.g., P(Y=1)) and the probability of a reference or pivot outcome (i.e.,
777 P(Y=4) in our case). This function is assumed to be linear in all explanatory variables,
778 including covariates and the specific SNP under consideration. Note that the beta
779 estimates (i.e., the log-odds ratios) are unique for each comparison. The polytomous
780 (multinomial) regression was performed using multinom in the R library nnet for the
781 three independent odds: P(Y=1)/P(Y=4), P(Y=2)/P(Y=4), and P(Y=3)/P(Y=4). Beta
782 estimates, standard errors, and p-values (two-sided, normal approximation) for the
783 remaining comparisons between phenotypic outcomes (i.e., P(Y=1)/P(Y=2),
784 P(Y=1)/P(Y=3), and P(Y=2)/P(Y=3)) were calculated from the model output such that,
785 e.g., $beta_{12} = beta_{14} - beta_{24}$ and $se_{12}^2 = se_{14}^2 + se_{24}^2$, where the first subscript denotes
786 the outcome of interest while the second subscript denotes the reference outcome.
787
788 To determine whether the lead SNPs were specific to one disease phenotype or shared
789 among phenotypes, we identified for which disease phenotype the OR was the highest
790 (we used the value of the OR rather than the most significant P-value in order not to

791 be influenced by the different power in the phenotype groups due to different sample-
792 sizes), and whether the OR was significantly (FDR ≤ 0.05) higher compared to the
793 other disease phenotypes. As a threshold for significance, we used an FDR
794 (Benjamini-Hochberg) value of 0.05, corresponding to a nominal P-value of < 0.017
795 in the three sets of cases vs cases analyses. In our analyses, an FDR adjustment is to
796 prefer (in favour of Bonferroni) due to its power to pinpoint as many positive findings
797 as possible, while retaining a low false-discovery rate (5% in our case).
798 Results were plotted as Venn diagrams to show the pair-wise overlap between disease
799 phenotypes. If two SNPs from the same locus that were not in LD with each other (R^2
800 <= 0.8) were assigned to the same area, the locus only occurs once in the Venn
801 diagram. However, for a few loci, multiple unlinked (R^2 <= 0.8) SNPs from the same
802 locus were assigned to different areas. Such loci were included at multiple locations
803 in the Venn diagram together with the name of the SNP (i.e., gene_SNP).
804
805 **Ethics**
806 UK Biobank was given ethical approval by the North West Multicentre Research
807 Ethics Committee, the National Information Governance Board for Health and Social
808 Care and the Community Health Index Advisory Group. UK Biobank holds a generic
809 Research Tissue Bank approval granted by the National Research Ethics Service
810 (http://www.hra.nhs.uk/) that lets applicants conduct research on UK Biobank data
811 without obtaining ethical approvals for each separate project. Access to UK Biobank
812 genetic and phenotypic data was given through the UK Biobank Resource under
813 Application Number 15479. All participants provided signed consent to participate in
814 UK Biobank.
815
816 **Data availability**

817 The genotypes and phenotypes included in the current study are available from the
818 UK Biobank data, which can be accessed by researchers upon application
819 (https://www.ukBiobank.ac.uk/). Summary statistics and codes used for this project
820 can be accessed by contacting the corresponding author.
821
822 **URLs**
823 UK Biobank, http://www.ukBiobank.ac.uk; PLINK, https://www.cog-
824 genomics.org/plink2 ; NHGRI-EBI GWAS Catalog, https://www.ebi.ac.uk/gwas/;
825 Software tool for LD Score estimation and estimation of variance components from
826 summary statistics, https://github.com/bulik/ldsc/; GCTA,
827 http://cnsgenomics.com/software/gcta/; BiomaRt, http://www.bioconductor.org;
828 GTEx, https://www.gtexportal.org/home/; DGIdb, http://www.dgidb.org/.
829
830 **Acknowledgement**
831 We acknowledge all the participants and the administrative staff at the UK Biobank.
832 The computations were performed on resources provided by SNIC through Uppsala
833 Multidisciplinary Centre for Advanced Computational Science (UPPMAX) under
834 projects b2016021, b2017059, sens2017538, and sens2017541. The work was
835 supported by grants from the Swedish Society for Medical Research (SSMF), the
836 Kjell and Märta Beijers Foundation, Göran Gustafssons Foundation, the Swedish
837 Medical Research Council (Project Number 2015-03327), the Marcus Borgström
838 Foundation, the Åke Wiberg Foundation, the Borgström Hedström Foundation and
839 the Swedish Heart-Lung Foundation.
840
841 **Author contributions**

Planned the study (WEE and ÅJ), analysed the data (WEE, ÅJ, TK), literature search (WEE), Figures (WEE, MRA, ÅJ), data interpretation (WEE, ÅJ, TK, MRA), writing of manuscript (WEE, ÅJ, TK, MRA).

846 **References**

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1064

Figure Legends

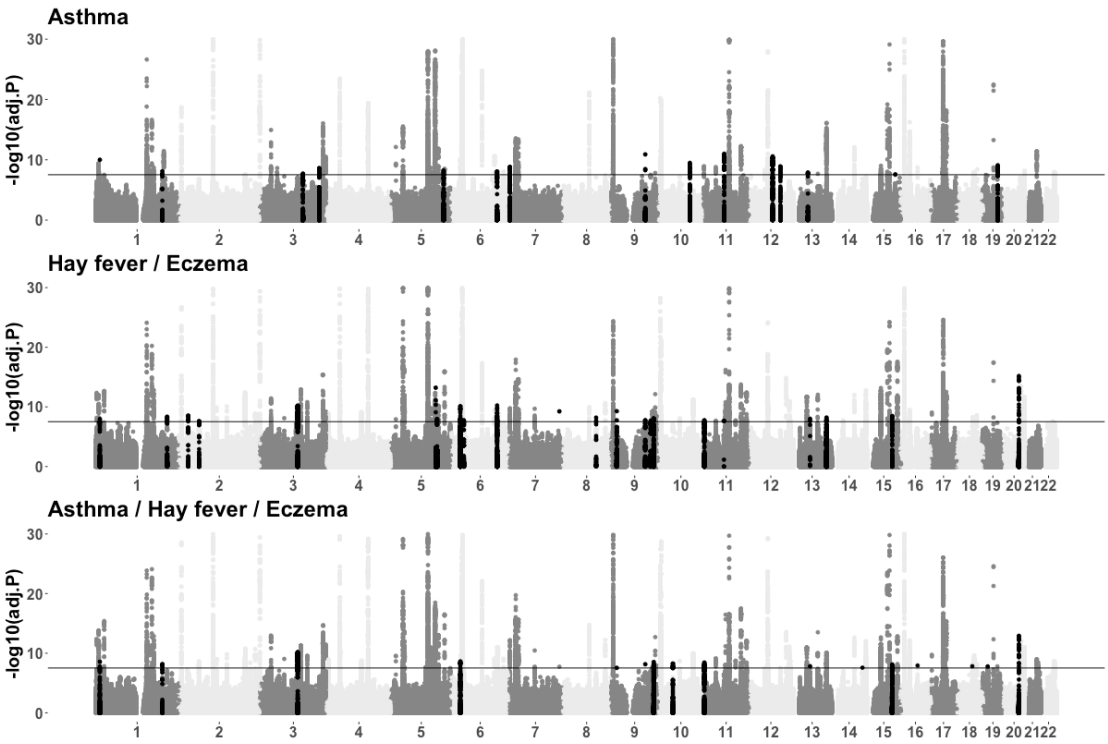

Figure 1. Manhattan plots for asthma, for hay fever and/or eczema, and for asthma and/or hay fever and/or eczema (combined) for autosomal chromosomes. The black horizontal line indicates the genome wide threshold ($3x10^{-8}$). The black regions represent novel loci found in this study.

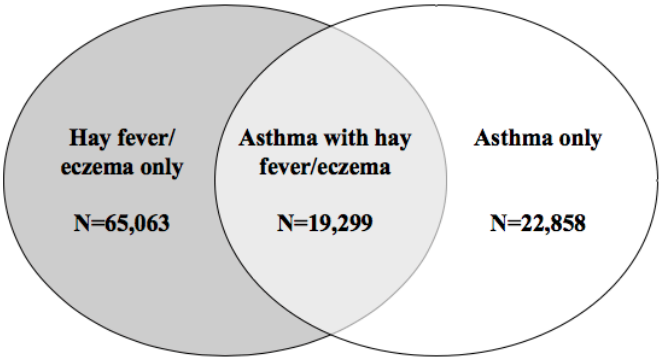

Figure 2. Comorbidity between asthma and hay fever/eczema.

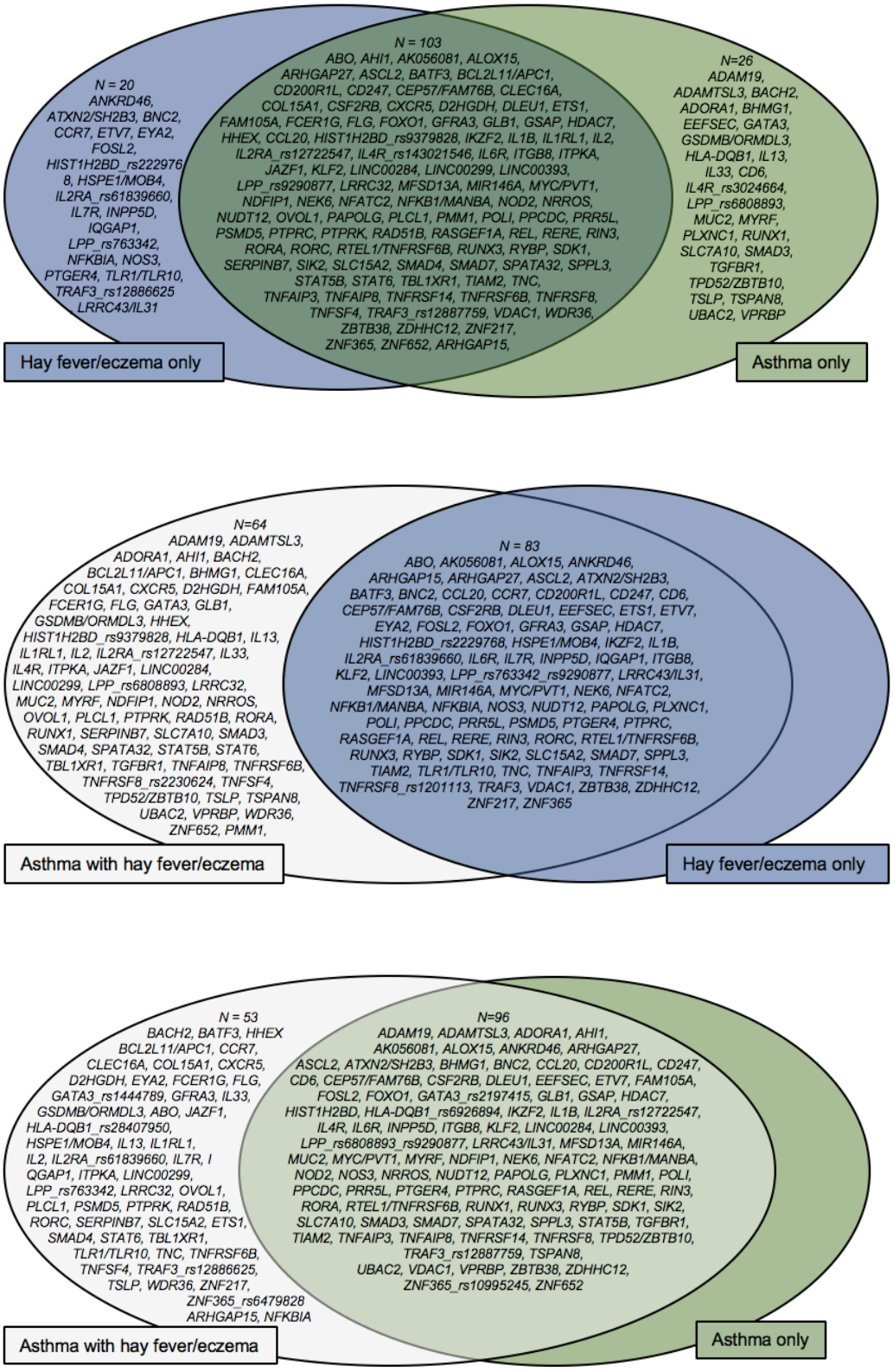

Figure 3. Venn diagram showing the phenotype-specificity of the GWA loci, based on the results from the polytomous logistic regression analyses. The Venn diagram show loci (SNPs) that are specific (significantly larger effect) to or shared between (no

significant difference in effects) between two non-overlapping groups of cases. The name of each locus is denoted by the most likely gene(s). At some of the loci (e.g. *IL2RA, LPP,* and *IL4R*), more than one independent (R2<0.8) lead SNP has been analysed in the polytomous logistic regression. If those showed different specificity pattern, they have been included twice in the figure with the name of respective lead SNP(s) also included in the locus name. P-values and estimates for the genes can be found in Table S16 where the area number 1 (green in the figure) indicates specificity for the asthma only, 2 (blue in the figure) specificity for hay fever/eczema only and area number 3 (white in the figure) specificity for asthma with hay fever/eczema (significantly larger estimate in the asthma with hay fever/eczema group of cases).

S1 Figure QQ-plot for Asthma in UK Biobank. The red line denotes the expected null-line of no association.

S2 Figure Regional plot for the missense variant rs2230624 in asthma.

S3 Figure QQ-plot for Hay fever and/or Eczema (combined) in UK Biobank. The red line denotes the expected null-line of no association.

S4 Figure Manhattan plots for Hay Fever and/or Eczema (combined), Hay Fever (only) and Eczema (only) analysed in UK Biobank for autosomal chromosomes. The black horizontal line indicates the genome wide threshold ($3x10^{-8}$). The black regions in the hay fever and/or eczema (combined) plot represent novel loci found in this study and the black regions in the hay fever (only) and eczema (only) plot represent two novel loci, not found in previous GWA studies or in our combined hay fever / eczema analysis.

S5 Figure QQ-plot for Hay fever (only) in UK Biobank. The red line denotes the expected null-line of no association.

S6 Figure QQ-plot for Eczema (only) in UK Biobank. The red line denotes the expected null-line of no association.

S7 Figure QQ-plot for Asthma and/or Hay fever and/or Eczema (combined) in UK Biobank. The red line denotes the expected null-line of no association.

Tables

Table 1. Baseline characteristics of Caucasian participants in UK Biobank.

	Asthma	Hay fever /eczema	Asthma/hay fever/eczema combined[b]	Hay fever	Eczema	Controls[c]
N Caucasians[a] (prior to QC)	51,645	102,862	130,865	22,919	9,578	294,477
N total included after QC[d]	41,934	84,050	106,772	18,915	7,884	239,773
N (%) males after QC	21,730 (51.8%)	42,639 (50.7%)	55,124 (51.6%)	8,692 (46.0%)	3,365 (42,7%)	138,666 (57.8%)
Age year span (mean)	38-70 (56.1)	39-72 (55.4)	38-72 (55.7)	40-77 (55.0)	40-70 (55.0)	39-73 (57.2)
Townsend deprivation index range (mean)	-6.3-10.6 (-1.3)	-6.3-10.6 (-1.6)	-6.3-10.6 (-1.5)	-6.3-10.4 (-1.7)	-6.3-9.6 (-1.9)	-6.3-10.9 (-1.5)
% Ever smoked (N yes / N no)	60.4% (31,040 / 20,390)	58.5% (59,983 / 42,616)	59.3% (77,335/53,121)	56.8% (12,986/9,879)	60.9% (5,815/3,737)	60.4% (177,212/116,275)

[a]The total number of Caucasians is N = 443,068.
[b]Asthma or hay fever and/or eczema combined as one phenotype.
[c]The same controls were used in all analyses.
[d] We removed first and second-degree relatives, using kinship data (estimated genetic relationship > 0.044), and participants with sex discordance, high heterozygosity, and participant with more than 5% missing SNP genotypes, resulting in 346,545 individuals after QC.

Table 2. Summary results for the 15 novel loci significantly associated with self-reported asthma in UK Biobank ($P \leq 3x10^{-8}$) with replication in the GABRIEL cohort.

lead SNP	locus[a] chr:start-end (kbp)	N snps (total[b]/ independent[c])	MAF[d]	Minor/ major allele	OR (95% CI) for minor allele	P	Likely target gene (s)	GABRIEL P OR (95% CI) for effective allele (minor/effective allele)
rs2230624	1:12,175-12,175	1/1	0.02	A/G	0.80 (0.75-0.86)	$1.01x10^{-10}$	*TNFRSF8*[e]	No proxy
rs2296618	1:198,656-198,670	5/1	0.13	G/A	0.93 (0.91-0.96)	$8.03x10^{-9}$	*PTPRC*[f]	No proxy
rs10934853	3:127,886-128,075	3/1	0.27	A/C	0.95 (0.94-0.97)	$2.20x10^{-8}$	*EEFSEC*[g]	P=0.006 OR=1.06 (1.02-1.11) A/C
rs6778937	3:176,708-176,868	28/1	0.28	C/T	0.95 (0.93-0.97)	$2.54x10^{-9}$	*TBL1XR1*[f]	No proxy
rs11466773	5:156,930-156,988	7/1	0.06	T/C	1.09 (1.06-1.13)	$6.32x10^{-9}$	*ADAM19*[g]	No proxy
rs2614266	6:135,691-135,818	6/1	0.44	A/T	1.05 (1.03-1.06)	$8.90x10^{-9}$	*AHI1*[f]	No proxy
rs10215232	7:3,062-3,153	12/1	0.12	G/C	0.93 (0.91-0.95)	$1.53x10^{-9}$	*SDK1*[f]	rs9986945[h], R^2=1.0[i] P=0.03 OR=1.07 (1.01-1.14) T/G
rs41283642	9:101,915-101,989	3/1	0.03	T/C	0.86 (0.82-0.90)	$1.27x10^{-11}$	*TGFBR1*[g]	No proxy
rs2497318	10:94,34-94,44	24/1	0.45	T/C	0.95 (0.94-0.97)	$3.21x10^{-10}$	*HHEX*[g]	Rs10882091[h], R^2=0.81[i] P=0.84 OR=1.00 (0.97-1.05) C/T
rs174535	11:61,543-61,623	49/1	0.35	C/T	0.95 (0.93-0.96)	$1.02x10^{-11}$	*MYRF*[e], *TMEM258*[g]	rs102275[h], R^2=1.0[i] P=0.045

								OR=1.04 (1.00-1.09) C/T
rs11178649	12:71,409-71,585	103/1	0.41	T/G	0.95 (0.93-0.96)	2.68×10^{-11}	*TSPAN8*[e]	rs1051334[h] R^2=1.0[i] P=0.04 OR=0.95 (0.92-0.99) (G/T)
rs4761592	12:94,556-94,604	17/1	0.15	T/C	0.93 (0.92-0.95)	1.27×10^{-9}	*PLXNC1*[f]	rs3912394[h], R^2=0.85[i] P=0.021 OR=1.07 (1.01-1.13) T/C
rs9316059	13:44,475-44,490	5/1	0.20	T/A	1.06 (1.04-1.08)	1.35×10^{-8}	*LINC00284*[f]	rs3764147[h], R^2=0.93[i] P=0.58 OR=1.01 (0.97-1.06) A/G
rs4842921	15:84,556-84,556	1/1	0.39	A/G	0.96 (0.94-0.97)	2.63×10^{-8}	*ADAMTSL3*[f]	No proxy
rs11671106	19:46,219-46,370	28/1	0.35	T/C	0.95 (0.94-0.97)	8.29×10^{-10}	*BHMG1*[e]	rs7250497[h], R^2=0.97[i] P=0.05 OR=1.04 (1.00-1.09) G/A

More details can be found in S1-S3 and S4 Tables.

[a] Defined as SNPs located < 1 Mb apart containing at least one significantly associated genetic variant at $P \leq 3 \times 10^{-8}$.

[b] Total number of SNPs with $P \leq 3 \times 10^{-8}$ within loci.

[c] Total number of independent associations within the locus, based on conditional analysis (14).

[d] Minor allele frequency.

[e] Lead SNP is in LD ($R^2 > 0.8$) with a missense variant.

[f] Gene(s) closest to the lead SNP.

[g] Lead SNP is in LD ($R^2 > 0.8$) with the lead eQTL SNP. Information on tissue type can be found in S3 Table.

[h] proxy SNP in LD (>0.8) with lead SNP.

[i] R^2 between lead SNP in UK Biobank and proxy SNP in GABRIEL.

Table 3. Summary results for the 22 novel loci significantly associated with self-reported hay fever and/or eczema in UK Biobank ($P \leq 3x10^{-8}$) with replication in the EAGLE cohort

Lead SNP	Locus[a] chr:start-stop (kbp)	N snps (total[b]/ independent[c])	MAF[d]	Minor/ major allele	P (OR)[e] [95%CI] hay fever/eczema	P (OR)[e] [95%CI] hay fever	P (OR)[e] [95%CI] eczema	Likely target gene	EAGLE P OR (95% CI) estimated for the minor allele (minor/major allele)
rs1201113	1:12,100-12,147	3/1	0.12	A/G	$1.05x10^{-8}$ (0.95) [0.93-0.97]	$4.67x10^{-3}$ (0.95) [0.92-0.99]	$1.69x10^{-2}$ (0.94) [0.90-0.99]	*TNFRSF*[f]	P=0.18 OR=1.04 (0.98-1.10) A/G
rs906363	1:212,858-212,877	6/1	0.15	C/T	$4.44x10^{-9}$ (1.05) [1.03-1.07]	$8.56x10^{-4}$ (0.97) [1.02-1.08]	$2.54x10^{-4}$ (1.09) [1.04-1.13]	*BATF3*[f]	$P=1.52x10^{-6}$ OR=1.19 (1.07-1.17) C/T
rs13405815	2:28,623-28,644	9/1	0.46	T/C	$3.01x10^{-9}$ (0.97) [0.95-0.98]	$4.04x10^{-5}$ (0.96) [0.94-0.98]	$3.70x10^{-3}$ (0.95) [0.92-0.98]	*RP11-373D23.3*[g]	Proxy rs6547850[h], R^2=1.0[i] P=0.0014 OR=0.95 (0.92-0.98) T/G
rs10185028	2:61,112-61,161	6/1	0.23	G/A	$2.74x10^{-8}$ (1.04) [1.03-1.05]	$9.47x10^{-4}$ (1.04) [1.02-1.07]	$1.17x10^{-2}$ (1.05) [1.01-1.09]	*REL*[f]	P=0.0007 OR=1.08 (1.03-1.12) G/A
rs11717778	3:112,526-112,693	144/1	0.34	A/G	$6.04x20^{-11}$ (0.96) [0.95-0.97]	$2.67x10^{-4}$ (0.96) [0.94-0.98]	$5.38x10^{-6}$ (0.92) [0.89-0.96]	*CD200R1L*[f]	P=0.0007 OR=0.94 (0.91-0.98) A/G
rs62379371	5:133,439-133,639	4/1	0.05	A/G	$6.08x10^{-14}$ (0.90) [0.87-0.92]	$7.83x10^{-6}$ (0.89) [0.84-0.94]	$4.18x10^{-5}$ (0.85) [0.78-0.92]	*TCF7*[f]	P=0.62 OR=0.95 (0.77-1.17) A/G
rs13185930	5:137,461-137,605	10/1	0.25	A/G	$1.12x10^{-8}$ (1.04) [1.03-1.05]	$3.19x10^{-2}$ (1.03) [1.00-1.05]	$4.64x10^{-1}$ (1.01) [0.98-1.05]	*GFRA3*[f]	P=0.42 OR=1.02 (0.98-1.06) A/G

rs2229768	6:25,823-26,239	24/1	0.24	C/T	$8.20x10^{-11}$ (1.05) [1.03-1.06]	$8.99x10^{-6}$ (1.06) [1.03-1.08]	$2.74x10^{-1}$ (1.02) [0.98-1.06]	*U91328.19* [g]	P=0.80 OR=1.00 (0.96-1.04) C/T
rs1998266	6:36,349-36,380	5/1	0.14	T/C	$1.70x10^{-8}$ (0.95) [0.94-0.97]	$1.23x10^{-3}$ (0.95) [0.92-0.98]	$1.68x10^{-3}$ (0.93) [0.88-0.97]	*ETV7* [f]	P=0.08 OR=0.95 (0.91-1.00) T/C
rs2746438	6:135,624-135,950	36/1	0.44	T/A	$5.70x10^{-11}$ (1.04) [1.03-1.05]	$9.24x10^{-7}$ (1.05) [1.03-1.08]	$2.73x10^{-5}$ (1.07) [1.04-1.11]	*AHI1* [f]	P=0.21 OR=1.02 (0.99-1.06) T/A
rs3918226	7:150,690-150,690	1/1	0.08	T/C	$5.65x10^{-10}$ (0.93) [0.91-0.95]	$1.54x10^{-7}$ (0.90) [0.86-0.93]	$6.09x10^{-1}$ (0.98) [0.93-1.05]	*NOS3* [f]	P=0.33 OR=1.04 (0.97-1.11) T/C
rs6986151	8:101,514-101,519	2/1	0.20	C/T	$6.19x10^{-9}$ (1.04) [1.03-1.06]	$5.39x10^{-6}$ (1.06) [1.04-1.09]	$2.44x10^{-3}$ (1.06) [1.02-1.11]	*ANKRD46* [f]	P=0.31 OR=1.00 (0.95-1.05) C/T
rs1330303	9:16,715-16,756	2/1	0.35	T/C	$5.21x10^{-10}$ (0.96) [0.95-0.97]	$2.95x10^{-8}$ (0.94) [0.92-0.96]	$3.90x10^{-1}$ (0.99) [0.95-1.02]	*BNC2* [f]	P=0.11 OR=1.01 (0.99-1.06) T/C
rs4743311	9:101,790-101,820	3/1	0.25	G/A	$1.69x10^{-8}$ (1.04) [1.03-1.05]	$7.93x10^{-6}$ (1.06) [1.03-1.08]	$1.27x10^{-1}$ (1.03) [0.99-1.07]	*COL15A1* [f]	P=0.88 OR=1.00 (0.96-1.04) G/A
rs12343737	9:117,804-117,834	2/1	0.10	T/C	$2.09x10^{-8}$ (0.95) [0.93-0.95]	$1.28x10^{-6}$ (0.92) [0.89-0.95]	$9.59x10^{-2}$ (0.96) [0.91-1.01]	*TNC* [f]	P=0.25 OR=0.97 (0.92-1.03) T/C
rs10986320	9:127,022-127,095	13/1	0.37	C/G	$8.81x10^{-9}$ (1.04) [1.02-1.05]	$4.13x10^{-5}$ (1.05) [1.02-1.07]	$7.32x10^{-2}$ (1.03) [1.00-1.07]	*NEK6* [f]	P=0.20 OR=0.98 (0.95-1.01) C/G

rs4076542	11:2,237-2,296	4/1	0.37	A/G	$1.74x10^{-8}$ (1.04) [1.02-1.05]	$4.40x10^{-3}$ (1.04) [1.02-1.06]	$7.78x10^{-1}$ (1.02) [0.98-1.05]	*ASCL2*[f]	P=0.70 OR=0.99 (0.96-1.03) A/G
rs4939490	11:60,793-60,793	4/1	0.39	G/C	$2.15x10^{-8}$ (0.97) [0.96-0.98]	$2.15x10^{-3}$ (0.97) [0.95-0.99]	$9.76x10^{-2}$ (0.97) [0.94-1.01]	*CD6*[f]	P=0.25 OR=1.02 (0.99-1.06) G/C
rs3116590	13:50,808-50,811	2/1	0.21	G/A	$1.00x10^{-8}$ (1.04) [1.03-1.06]	$1.11x10^{-2}$ (1.03) [1.01-1.06]	$7.24x10^{-3}$ (1.05) [1.01-1.10]	*DLEU1*[f]	P=0.38 OR=1.02 (0.98-1.06) G/A
rs4771332	13:99,839-100,070	7/1	0.31	T/C	$6.21x10^{-9}$ (0.96) [0.95-0.98]	$6.09x10^{-3}$ (0.97) [0.95-0.99]	$1.29x10^{-1}$ (0.97) [0.94-1.01]	*UBAC2*	P=0.40 OR=0.98 (0.95-1.02) C/T
rs4381563	15:75,399-75,448	7/1	0.34	A/T	$3.37x10^{-9}$ (0.96) [0.95-0.98]	$2.98x10^{-3}$ (0.97) [0.95-0.99]	$3.37x10^{-2}$ (0.96) [0.93-1.00]	*PPCDC*[f]	P=0.89 OR=1.00 (0.97-1.04) A/T
rs6066184	**20:45,232-45,716**	**33/1**	**0.26**	**G/C**	**$6.55x10^{-16}$ (0.95) [0.93-0.96]**	**$5.25x10^{-11}$ (0.92) [0.90-0.94]**	**$2.03x10^{-2}$ (0.96) [0.92-0.99]**	***EYA2*[f]**	**P=0.02 OR=1.05 (1.01-1.09) G/C**

More details can be found in S3 and S5-S7 Table.

[a] Defined as SNPs located < 1 Mb apart containing at least one significantly associated genetic variant at $P \leq 3x10^{-8}$.

[b] Total number of SNPs with $P \leq 3x10^{-8}$ within loci.

[c] Total number of independent associations within the locus, based on conditional analysis (14).

[d] Minor allele frequency.

[e] OR for minor allele.

[f] Gene(s) closest to the lead SNP.

[g] Lead SNP is in LD ($R^2 > 0.8$) with the lead eQTL SNP. Information on tissue type can be found in S3 Table.

[h] proxy SNP in LD (>0.8) with lead SNP.

[i] R^2 between lead SNP in UK Biobank and proxy SNP in EAGLE.

Table 4. Summary results for the 16 novel loci significantly associated with self-reported asthma and/or hay fever and/or eczema (combined) in UK Biobank ($P \leq 3x10^{-8}$).

Lead SNP	Locus[a] chr:start-stop (kbp)	N snps (total[b]/ independent[c])	MAF[d]	Minor/ major allele	P (OR[e]) [95%CI] combined	P (OR[e]) [95%CI] asthma	P (OR[e]) [95%CI] hay fever/ eczema	Likely target gene
rs2230624	1:12,080-12,175	2/2	0.02	A/G	$2.64x10^{-9}$ (0.87) [0.84-0.91]	$1.01x10^{-10}$ (0.80) [0.75-0.86]	$1.99x10^{-7}$ (0.88) [0.84-0.92]	*TNFRSF8*[f]
rs7410883	1:198,640-198,670	5/1	0.11	C/T	$7.00x10^{-9}$ (0.95) [0.93-0.97]	$2.26x10^{-8}$ (0.93) [0.91-0.95]	$1.78x10^{-6}$ (0.96) [0.94-0.97]	*PTPRC*[g]
rs9816107	3:112,526-112,693	160/1	0.34	A/C	$6.80x10^{-11}$ (0.96)	$1.51x10^{-6}$ (0.96) [0.95-0.97]	$8.39x10^{-11}$ (0.96) [0.95-0.97]	*CD200R1L*[g]
rs62379371	5:133,439-133,639	4/1	0.05	A/G	$1.13x10^{-13}$ (0.91) [0.89-0.93]	$1.23x10^{-7}$ (0.91) [0.88-0.94]	$6.08x10^{-14}$ (0.90) [0.87-0.92]	*VDAC1*[g]
rs9379828	6:26,038-26,184	13/1	0.37	G/C	$2.71x10^{-9}$ (1.03) [1.02-1.05]	$1.07x10^{-10}$ (1.05) [1.04-1.07]	$1.42x10^{-6}$ (1.03) [1.02-1.04]	*HIST1H2BD*[h]
rs1330303	9:16,715-16,715	1/1	0.35	T/C	$2.84x10^{-8}$ (0.97) [0.96-0.98]	0.016 (0.98) [0.97-1.00]	$5.21x10^{-10}$ (0.96) [0.95-0.97]	*BNC2*[g]
rs41283642	9:101,915-101,915	1/1	0.03	T/C	$7.03x10^{-9}$ (0.92) [0.89-0.94]	$1.27x10^{-11}$ (0.86) [0.82-0.90]	$6.42x10^{-6}$ (0.93) [0.90-0.96]	*TGFBR1*[g]
rs3758212	9:127,002-127,178	14/1	0.37	T/C	$2.99x10^{-9}$ (1.03) [1.02-1.05]	$1.80x10^{-5}$ (1.04) [1.02-1.05]	$2.18x10^{-8}$ (1.04) [1.02-1.05]	*NEK6*[g]
rs2505504	**10:43,728-43,763**	**17/1**	**0.29**	**A/G**	**$5.45x10^{-9}$ (1.04)** [1.02-1.05]	**$1.96x10^{-6}$ (1.04)** [1.02-1.06]	**$4.61x10^{-7}$ (1.03)** [1.02-1.05]	***RASGEF1A***[g]

rs7114923	11:2,237-2,305	21/1	0.37	T/C	$3.74x10^{-9}$ (1.03) [1.02-1.05]	$1.20x10^{-5}$ (1.04) [1.02-1.05]	$2.65x10^{-8}$ (1.04) [1.02-1.05]	*ASCL2*[g]
rs3116590	13:50,808-50,808	1/1	0.21	G/A	$1.52x10^{-8}$ (1.04) [1.03-1.05]	0.0064 (1.03) [1.01-1.05]	$1.00x10^{-8}$ (1.04) [1.03-1.06]	*DLEU1*[g]
rs61975764	**14:93,014-93,014**	**1/1**	**0.47**	**A/G**	**$2.65x10^{-8}$ (1.03) [1.02-1.04]**	**$1.46x10^{-7}$ (1.04) [1.03-1.06]**	**$7.84x10^{-7}$ (1.03) [1.02-1.04]**	***RIN3***[g]
rs4381563	15:75,275-75,448	19/1	0.33	A/T	$7.81x10^{-9}$ (0.97) [0.96-0.98]	0.00027 (0.97) [0.96-0.99]	$3.37x10^{-9}$ (0.96) [0.95-0.97]	*PPCDC*[g]
rs12956924	**18:46,451-46,451**	**1/1**	**0.31**	**A/G**	**$1.52x10^{-8}$ (1.03) [1.02-1.05]**	**$2.64x10^{-5}$ (1.04) [1.02-1.05]**	**$2.09x10^{-7}$ (1.03) [1.02-1.05]**	***SMAD7***[g]
rs10419921	**19:16,412-16,412**	**1/1**	**0.30**	**T/C**	**$1.67x10^{-8}$ (1.03) [1.02-1.05]**	**$5.62x10^{-6}$ (1.04) [1.02-1.06]**	**$1.09x10^{-6}$ (1.03) [1.02-1.04]**	***KLF2***[g]
rs6066184	20:45,228-45,716	26/2	0.26	G/C	$1.19x10^{-13}$ (0.95) [0.94-0.97]	$4.27x10^{-6}$ (0.96) [0.94-0.98]	$6.55x10^{-16}$ (0.95) [0.93-0.96]	*EYA2*[d]

Loci found only when analysing all three diseases as one phenotype are marked as bold. More details can be found in S3, S12-S13 and S15 Tables.

[a] Defined as SNPs located<1 Mb apart containing at least one significantly associated genetic variant at $P \leq 3x10^{8}$.

[b] Total number of SNPs with $P \leq 3x10^{-8}$ within loci.

[c] Total number of independent associations within the locus, based on conditional analysis (14).

[d] Minor allele frequency.

[e] OR for minor allele.

[f] Lead SNP is in LD ($R^2 > 0.8$) with a missense variant.

[g] Gene(s) closest to the lead SNP.

[h] Lead SNP is in LD ($R^2 > 0.8$) with the lead eQTL SNP. Information on tissue type can be found in S3 Table.

Table 5. SNP-based heritability in UK Biobank for asthma and hay fever/eczema (combined as one phenotype) estimated with LDSC (19).

			Prevalence used in LD-score[a]		(A) All SNPs		(B) Without significant loci		h2 explained by significant loci
Phenotype	**N cases**	**N controls**	**Population**	**Sample**	**h2**	**SE**	**h2**	**SE**	**Absolute terms: (A) - (B)**
Asthma	41,926	239,751	0.117	0.117	0.210	0.017	0.168	0.010	0.042
Hay fever/ Eczema	84,034	239,751	0.232	0.232	0.160	0.010	0.124	0.007	0.036

[a]LDSC requires values for population and sample prevalence when estimating SNP heritability. In these analyses we used the prevalence in the UK Biobank cohort (Table 1) as the sample prevalence. However, due to the cross-sectional design of the UK Biobank we used the same values as population prevalence.

Abbreviations

SNP Single nucleotide polymorphism

GWA study Genome Wide Association Study