1 Comorbidities of keloid and hypertrophic scars in UK Biobank

2 **Title:** Comorbidities of keloid and hypertrophic scars in UK Biobank

3 **Subtitle:** Comorbidities of excessive scarring

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20 **Conflicts of interest:** None

21 **Date of revision:** 20th October 2022

22 **Word count:** 3227

23

Key points

Question: What diseases are people with keloid and hypertrophic scars (excessive scarring) at risk of?

Findings: This cross-sectional UK Biobank study identified associations of excessive scarring with hypertension, vitamin D deficiency and atopic eczema. Atopic eczema was also significantly associated when accounting for confounders, and the associations varied with ethnicity. A phenome-wide scan of this predominantly white cohort identified a range of previously unreported correlations; musculoskeletal disease and pain symptoms were prominent non-dermatological associations.

Meaning: Excessive scarring may share underlying predispositions with systemic diseases; future research should aim to understand whether there are causal relationships linking the observed associations.

Tweet

What diseases associate with keloid/hypertrophic scars? This UK Biobank study confirmed excessive scarring associates with hypertension, vitamin D deficiency and atopic eczema, and discovered musculoskeletal disease & pain symptoms are also comorbidities.

Abstract

Importance: Keloids and hypertrophic scars (excessive scarring) are relatively understudied disfiguring chronic skin conditions with high treatment resistance.

Objective: To evaluate established comorbidities of excessive scarring in Europeans, with comparisons across ethnic groups, and to identify novel comorbidities via a phenome-wide association study (PheWAS).

Design: This cross-sectional study used UK Biobank (UKB) data and fitted logistic regression models for testing associations between excessive scarring and a variety of outcomes, including previously studied comorbidities and 1518 systematically defined disease categories. Additional modelling was performed within subgroups of participants defined by self-reported ethnicity.

Setting: Multi-centre population-based cohort study.

Participants: Of 502701 UKB participants, analyses were restricted to 230078 individuals with linked primary care records.

Exposures: Keloid or hypertrophic scar diagnoses

Main outcomes and measures: Previously studied disease associations (hypertension, uterine leiomyoma, vitamin D deficiency, atopic eczema) and phenotypes defined in the PheWAS Catalog.

Results: Of the 972 people with excessive scarring, there was a higher proportion of females compared to the 229106 controls (65% versus 55%) and a lower proportion of white ethnicity (86% versus 95%). Associations were identified with hypertension, vitamin D deficiency and atopic eczema in models accounting for age, sex and ethnicity, and the association with atopic eczema (Odds Ratio (OR) 1.68, p<0.001) was remained statistically significant after accounting for additional potential confounders. Fully-adjusted analyses within ethnic groups revealed associations with hypertension in black participants (OR 2.05, p=0.019) and with vitamin D deficiency in Asian participants (OR 2.24, p=0.006). The association with uterine leiomyoma was borderline significant in black women (OR 1.93, p=0.05) whereas the association with atopic eczema was significant in white participants (OR 1.68, p<0.001) and showed a similar trend in Asian (OR 2.17, p=0.048) and black participants (OR 1.89, p=0.13). The PheWAS identified 110 significant associations across disease systems; of the non-dermatological, musculoskeletal disease and pain symptoms were prominent.

66   Conclusions and Relevance: We validated comorbidities of excessive scarring in an independent

67   cohort with comprehensive coverage of health outcomes. We also documented additional phenome-

68   wide associations that will serve as a reference for future studies to investigate common underlying

69   pathophysiologic mechanisms.

70

Introduction

Keloids and hypertrophic scars are chronic disfiguring manifestations of excessive cutaneous wound healing considered prototypic of skin fibrosis.[1–3] Whether they are distinct entities or a quantitative extreme of normal wound scars remains an active area of debate.[4] Both conditions involve excess extracellular matrix deposition and raised scar tissue, but unique to keloids are horizontal expansion of scars and absence of clinical regression. Common to both are high symptom burden[5,6] and lack of universally effective treatment.[7,8]

There is increasingly a shift from single-disease focused research towards studying disease systems.[9] Understanding disease comorbidities has both biological and clinical benefits, such as highlighting novel mechanisms and offering opportunities for targeted and early clinical intervention. Previous studies of keloid and hypertrophic scar comorbidities have been limited to candidate diseases, based on speculated biological[10–15] or demographic similarities.[16,17]

In this study, we comprehensively assessed disease associations of keloids or hypertrophic scars (henceforth excessive scarring) in UK Biobank (UKB), a multi-centre population-based longitudinal observational study of >500,000 participants including >950 with a diagnosis of excessive scarring. We performed multivariable logistic regression analyses for previously-studied comorbidities across several ethnic groups and carried out a phenome-wide association study (PheWAS) over a wide range of systematically-defined diseases.

Methods

This project used UKB data under project number 15147. The UKB study was approved by the National Health Service National Research Ethics Service (11/NW/0382).

Study population

UKB is a large population-based prospective cohort study that recruited >500,000 participants (40-69 years at recruitment) who attended 1 of 22 assessment centers across the UK from 2006-2010.[18] Volunteers provided written informed consent for their participation. Rich health-related information

96   is available, including regularly updated self-reported health conditions, lifestyle indicators,

97   anthropometric and biological measurements. Longitudinal health record data is available, including

98   hospital episode statistics and primary care data. Participants were also asked to report their ethnicity

99   based on a set of predefined ethnic categories, further detailed in

100 https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=21000. We restricted our analyses to individuals

101 with linked-primary care records (limiting the possibility of misclassifying participants as unaffected

102 due to missing data).

103 Ascertainment of disease status

104 Clinical code selection - Disease status was ascertained through the following data sources: self-

105 reported (verbal interview), linked-hospital episode statistics [International Classification of Diseases

106 (ICD), ninth and tenth revisions], cancer register (ICD9 and ICD10), primary care records (Read2 and

107 Read3), and the Office of Population Censuses and Surveys Classification of Interventions and

108 Procedures (OPCS4). Clinical codelists were manually curated by study authors (CYU, ANW) for

109 excessive scarring (described below), vitamin D deficiency and atopic eczema (Supplementary Table

110 2). For conditions with pre-existing manually-curated codelists (hypertension, uterine leiomyoma),

111 Read2 and ICD10 clinical codelists were obtained from the CALIBER portal.[21] These clinical codelists

112 (Supplementary Table 2) were minimally adapted and mapped to Read3 and ICD9 equivalents

113 respectively, using UKB Resource 592 (https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=592).

114 Excessive scarring status - A broad definition of "excessive scarring" was used, constituting a diagnosis

115 of keloid or hypertrophic scar, which can be difficult to clinically differentiate[19,20] and are not well-

116 distinguished by electronic health record (EHR) coding systems. Primary care data included diagnostic

117 codes specific to either keloid or hypertrophic scar whereas those from linked-hospital episodes

118 statistics could pertain to either scar type. The final codes selected were: 7014 (ICD9), L910 (ICD10),

119 7L19A (Read2), M218. (Read2), M214. (Read2 and Read3), M2y11 (Read2), XaC07 (Read3), XaPxn

120 (Read3) and X78TS (Read3; Supplementary Table 2). Within this group, we additionally identified

121 individuals who had likely received scar-related treatment to define a more homogenous cohort

122 with moderate-to-severe scarring (hereafter "treated excessive scarring"), defined by codes for scar

123 excision/refashioning and triamcinolone treatment (Supplementary Table 3).

124 Comorbidities/outcomes - A systematic search for excessive scarring disease associations was

125 performed on Medline using the following query: (case-control studies/ or cohort studies/ or (Risk

126 Factors or (comorbidity or Comorbidity) or comorbidities or (Prevalence or prevalence) or association

127 or predispose or risk).mp.) and (hypertrophic scar.mp. or Cicatrix, Hypertrophic/ or ((Keloid or keloid

128 or keloids) not Acne Keloid).m_titl.). This resulted in 708 references that were independently

129 reviewed for relevance. From the 21 remaining references (Supplementary Table 1), disease

130 associations selected for analysis were those studied in ≥2 independent reports, namely

131 hypertension, uterine leiomyoma, vitamin D deficiency and atopic eczema.

132 PheWAS - We used the PheWAS Catalog with phecodes that represent a single phenotype and

133 corresponding groupings.[22] The same data sources used for clinical code selection were mapped to

134 ICD10 codes and subsequently mapped to 1518 phecodes using Phecode Map 1.2.

135 Statistical analyses

136 Descriptive statistics are presented as frequencies with percentages for categorical variables and

137 means with standard deviations for continuous variables. Pearson's Chi-squared test and Welch's t-

138 test were used for comparisons between categorical and continuous variables, respectively. Statistical

139 significance was set at $p<0.05$.

140 Significant comorbidity associations were further examined using multivariable logistic regression

141 analyses to estimate odds ratios (OR) and 95% confidence intervals (CIs). In each model, excessive

142 scarring was the exposure variable, and the comorbidity was the outcome. As we were testing four

143 primary comorbidities (hypertension, uterine leiomyoma, vitamin D deficiency, atopic eczema), a

144 Bonferroni-adjusted p-value threshold (0.05/4=0.0125) was used.

145 We noted 3403 individuals (1.2% of the study cohort) with missing data for at least one of age, sex,

146 ethnicity, Townsend Deprivation Index (TDI), body mass index (BMI) or smoking status. Participants

147 with missing data were more likely to be male and of non-white ethnicity, with higher TDI and BMI

148 (Supplementary Table 4). There were no significant differences in missingness between participants

149 with and without excessive scarring diagnoses(Supplementary Table 5). Nevertheless, for testing

150 associations, the full cohort of 230078 participants was analysed and multiple imputation (20 imputed

151 datasets) was used to account for missing data.[23]

152 To investigate the independent association with excessive scarring, a "minimal model" adjusting for

153 age, sex (except uterine leiomyoma, which was restricted to female participants only, n=125771) and

154 ethnicity, and a "full model" adjusting for the additional potential confounding covariates were fitted

155 for each disease association. The additional covariates were: (1) hypertension: BMI, TDI, smoking

156 status, diabetes, hyperlipidaemia[24] (2) uterine leiomyoma: BMI[25,26], TDI, smoking status (3)

157 vitamin D deficiency: BMI, TDI, smoking status[27,28] and (4) atopic eczema: BMI, TDI, allergic

158 rhinitis, asthma[29].

159 To assess whether the disease associations varied by ethnicity, separate fully-adjusted logistic

160 regressions were fitted in the three largest ethnic groups. These comprised self-reported white

161 participants (85.9%), black or black British participants (henceforth "black participants", 6.4%) and

162 Asian or Asian British participants (henceforth "Asian participants", 5.2%), as described in Study

163 Population. To assess whether any differences in OR across ethnicities could be attributable to

164 chance, the analysis was repeated in the full cohort with an interaction term between excessive

165 scarring status and ethnicity.

166 For the PheWAS, logistic regressions were performed to assess the association between excessive

167 scarring and the prevalence of each phecode diagnosis, adjusting for age, sex, ethnicity, smoking

168 status, BMI and TDI. A Bonferroni-adjusted p-value threshold of $0.05/1518=3.3×10^{-5}$ was used.

169 Phecodes with <200 cases or controls were excluded.

170 All statistical analyses were performed with R version 4.1.2. Specific R packages included mice,[23]

171 gtsummary,[30] tidyverse, [31] flextable,[32] PheWAS,[33] targets,[34] ukbwranglr[35] and

172 codemapper.[36]

Results

174 We analysed 230078 UK Biobank participants for whom linked GP data were available

175 (Supplementary Figure 1). 972 participants had a record of excessive scarring (740 with a diagnostic

176 code specific for keloid, 110 specific for hypertrophic scar, 177 for either keloid or hypertrophic scar;

177 Supplementary Figure 2). The prevalence of excessive scarring for the three largest ethnic groups

178 were: 1.1% (Asian), 2.4% (black) and 0.4% (white). Table 1 shows the baseline characteristics for the

179 excessive scarring and comparator groups. In the excessive scar-affected group, there was a higher

180   proportion of females than in the unaffected group (65% versus 55%) and a lower proportion of

181   participants with self-reported white ethnicity (86% versus 95%). Of the 972 participants with

182   excessive scarring, 106 had a record of scar-related treatment. There were no notable differences in

183   baseline characteristics between these participants and those without a record of scar-related

184   treatment (Supplementary Table 6).

185   Previously studied associations with excessive scarring

186   All previously studied comorbidities (hypertension, uterine leiomyoma, vitamin D deficiency, atopic

187   eczema) were more prevalent for individuals with excessive scarring (Table 1). Vitamin D deficiency

188   and atopic eczema were around twice as common in the excessive scar cohort: 5.1% versus 2.4%

189   (vitamin D deficiency) and 10% versus 5.9% (atopic eczema). The higher prevalence for uterine

190   leiomyoma and hypertension was less marked: 15% versus 11% (leiomyoma) and 37% versus 34%

191   (hypertension). We found no evidence for differences in prevalence of the primary comorbidities

192   between treated excessive scarring cases and the rest of the excessive scarring group (Supplementary

193   Table 6) but with fewer cases, no statistically significant associations were observed when considering

194   the treated excessive scarring subgroup against the whole unaffected cohort (Supplementary Table

195   7).

196   Each comorbidity was analysed as a disease outcome using two multivariable logistic regression

197   models: minimally-adjusted (for age, sex and ethnicity except for uterine leiomyoma which was tested

198   within females only adjusting for age and ethnicity) and fully-adjusted (with additional potential

199   confounders for each comorbidity; Table 2). Statistically significant associations with excessive

200   scarring were observed for hypertension and atopic eczema in the minimally-adjusted models, while

201   the association with vitamin D deficiency fell short of Bonferroni-corrected significance (OR 1.42 (95%

202   CI 1.05-1.93), p=0.02). In fully-adjusted models, only the association with atopic eczema (OR 1.68

203   (95% CI 1.36-2.07), p<0.001) remained significant. Despite a positive effect-size estimate, there was

204   no significant association between excessive scarring and uterine leiomyoma (OR 1.19 (95% CI 0.95-

205   1.49), p=0.13).

206   We then performed association testing within subgroups of participants defined by self-reported

207   Asian (53 excessive scar affected, 4654 unaffected), black (61 affected, 2448 unaffected), and white

208   (829 affected, 217502 unaffected) ethnicity (Table 3A). With the exception of atopic eczema, our

209   analysis suggested a divergence between ethnic groups in the prevalence of each comorbidity and its

210   association with excessive scarring (Table 3B). The associations with hypertension and uterine

211   leiomyoma were nominally significant in black participants [OR 2.05 (95% CI 1.13-3.72), p=0.019

212   (hypertension) and OR 1.93 (95% CI 1.00-3.71), p=0.05 (uterine leiomyoma)] and not significant in

213   Asian or white participants. Vitamin D deficiency was only significantly associated with excessive

214   scarring in Asian participants (OR 2.24 (95% CI 1.26-3.97), p=0.006). For atopic eczema, the

215   association with excessive scarring was highly significant in white participants (OR 1.68 (95% CI 1.34-

216   2.12), p<0.001), nominally significant in Asian participants (OR 2.17 (95% CI 1.01-4.67), p=0.048), and

217   although not statistically significant in black participants, exhibited a similar trend (OR 1.89 (95% CI

218   0.83-4.28), p=0.13). Finally, to formally assess these differences we fitted a full logistic regression

219   model incorporating an interaction between excessive scarring status and ethnicity, finding statistical

220   evidence for ethnicity-specific effect sizes in the case of hypertension in black participants (relative to

221   white participants, p=0.049).

222   Discovery analysis

223   We screened 1518 phecodes across 17 disease groups, identifying 110 diseases significantly enriched

224   among participants with excessive scarring (Figure 1, Table 4, Supplementary Table 8).

225   There was strongest evidence of association for several dermatological diseases, most prominently

226   sebaceous cyst (OR 2.56, $p=9.45 \times 10^{-30}$), non-epithelial skin cancer (OR 2.89, $p=2.03 \times 10^{-25}$) and the

227   umbrella phenotype "diseases of hair/hair follicles" (OR 2.3, $p=1.50 \times 10^{-22}$), as well as infections of

228   skin/subcutaneous tissue, seborrheic keratosis, actinic keratosis, acne, and notably, atopic/contact

229   dermatitis, all with OR>1.9 and $p<1.0 \times 10^{-11}$. Similarly strong evidence was observed for pain-related

230   symptoms, particularly for joint pain (OR 1.84, $p=1.87 \times 10^{-20}$) but also back pain, cervicalgia,

231   enthesopathies and mastodynia, all with OR>1.6 and $P< 1.0 \times 10^{-12}$. Significant associations with the

232   largest effect sizes were abnormal weight gain (OR 3.97, $p=9.32 \times 10^{-8}$) and heart valve replacement

233   (OR 3.9, $p=6.65 \times 10^{-7}$).

234   Associations were identified with hypertension (OR 1.26, $p=2.05 \times 10^{-3}$) and vitamin D deficiency (OR

235   1.47, $p=1.34 \times 10^{-2}$) as expected, but these did not meet Bonferroni-corrected significance. Other

236   previously reported associations that did not meet our selection criteria for specific analysis were

237   explored, including obesity, osteoporosis, skin cancers, pancreatic cancer, migraine and asthma

238 (Supplementary Table 1). Of these, statistically significant associations were observed for skin cancers

239 (melanoma, OR 3.17, p=3.33x10^{-11}) and migraine (OR 1.53, p=6.29x10^{-6})(Supplementary Table 9).

Discussion

241 To date there have been few large-scale association studies for excessive scarring.[10–13,15] This

242 study aimed to both validate previously studied associations (hypertension,[16,37,38] uterine

243 leiomyoma,[13,17] vitamin D deficiency[14,15] and atopic eczema[11,12]) as well as scan for

244 excessive scarring associations across the phenome. Our ethnicity-specific analysis represents the first

245 comprehensive study of excessive scarring in white people, the most-represented ethnic group in

246 UKB.

247 In the trans-ethnic UKB population, we replicated associations with three (hypertension, vitamin D

248 deficiency and atopic eczema) of the four primary comorbidities previously studied two or more

249 times. Only the associations with hypertension and atopic eczema were statistically significant after

250 correcting for multiple tests. The association with hypertension was attenuated after adjusting for

251 additional risk factors (BMI, TDI, smoking status, diabetes, hyperlipidaemia). This suggests the

252 observed difference in hypertension prevalence is linked to differences in these risk factors between

253 people with and without excessive scarring. However, in our cross-sectional analysis we are unable to

254 determine the causal relationship between excessive scarring and increased hypertension risk factor

255 burden.

256 Subgroup analyses revealed possible ethnic variations in comorbidity risk, particularly for

257 hypertension in black participants, in whom we found a significantly larger effect size than in white

258 participants. Although our relatively small subgroup sample sizes make robust interpretation

259 challenging, given the well-established disproportionate burden of diseases within the respective

260 ethnic groups,[25,39–41] we propose that there may be ethnicity-specific risk determinants that are

261 shared by these pathologies. For example, vascular dysfunction is thought to contribute to the severe

262 hypertension and hypertensive heart failure specifically affecting the black population.[42,43]

263 Abnormal endothelial function and microvascular architecture are also observed in keloids.[47]

264 Replication of these findings in a larger cohort may make a case for the early identification of

265 cardiovascular disease in black individuals with excessive scarring.

266   The only association that showed nominally significant evidence for association in multiple ethnic

267   groups was atopic eczema. Interestingly, this has previously been reported in Taiwanese[12] and

268   Korean[11] populations, and we now observe this association across all three of our broadly defined

269   ethnic groupings; however, regional variations in disease prevalence and associations may still

270   emerge. Atopic eczema skin is more likely to be excoriated and scars may thus be an epiphenomenon.

271   Nevertheless, our result adds epidemiological support to the hypothesis that the Th2 inflammatory

272   axis contributes to keloid pathogenesis.[48]

273   Previous non-genetic applications of PheWAS's[54–57] have been based only on ICD diagnostic codes.

274   This would have excluded a large proportion of our cases who were only identified through primary

275   care codes. Through our comprehensive strategy to maximize identification of people with excessive

276   scarring, we highlighted numerous significant disease associations, potentially indicating an increased

277   risk of poorer health outcomes.

278   The frequent female genitourinary disease associations are consistent with suggestions that sex

279   hormones may play a role in keloid pathophysiology.[58–60] Potentially, this could be explained by

280   the over-representation of female participants within the excessive scar-affected group; however, our

281   models adjusted for sex. The highly significant associations with dermatological conditions and

282   neoplasms may represent true predispositions or reflect ascertainment bias (i.e. if a patient presents

283   with a dermatological condition or is reviewed post-surgically, a scar-related diagnosis is more likely

284   to be recorded).

285   Of the dermatological associations, diseases of the pilosebaceous unit (sebaceous cyst, diseases of

286   hair/hair follicles, acne) support the 'sebum hypothesis'[61] which is based on high sebaceous gland

287   density observed in keloid-prone skin[62] and sebum being intrinsically pro-inflammatory.[63] The

288   association of keloid with skin cancer has been previously reported.[10] Although plausible reasons

289   have been proposed including similar bioenergetics (reliance on glycolysis)[64,65] and signalling

290   pathways including TGFβ/Smad[66–68] and Wnt/beta-Catenin,[69–72] this finding is interpreted

291   cautiously, again considering the risk of ascertainment bias.

292   The associations with musculoskeletal disorders (enthesopathy, pain in joint, back pain, cervicalgia)

293   may support the observation of chondrogeneic misdifferentiation in keloids[73] and the shared

294   significance of TGFβ in joint pathologies.[74,75] Interestingly, associations with pain symptoms

295   spanned disease categories (non-specific chest pain, irritable bowel syndrome, mastodynia, acute

296   pain, headache syndromes, pain in joint, back pain, cervicalgia). Pain is known to debilitate some

297   keloids sufferers; [76] whether there is shared underlying biopsychosocial dysfunction with other pain

298   entities or whether they may be mutually reinforcing is speculative. Nonetheless, chronic pain

299   represents a major global burden of disease[77] and proactive identification of these conditions may

300   aid patient counseling and treatment decisions.

301   Finally, whether an individual whose skin scars excessively is at risk of excessive internal scarring

302   remains unanswered. In our study, the association of peritoneal adhesions with excessive scarring

303   carried an OR of 3.68 ($p=1.19 \times 10^{-4}$), which is intriguing but this is based only on 617 cases of

304   peritoneal adhesions, nine of whom had excessive scarring.

Limitations

306   Although this study utilized a large biobank cohort, a relatively small sample size of excessive scarring

307   cases were identified (n=972). This is particularly relevant when attempting to dissect differences

308   between ethnic groups, as there is less statistical power to detect significant associations in groups

309   with lower sample numbers. However, it is reassuring that disease prevalence in our dataset is in

310   keeping with currently available epidemiological studies.[59] As most participants report white

311   ethnicity, the main findings, particularly from the PheWAS, may not be generalizable to other ethnic

312   groups for whom excessive scarring is a more prominent issue.

313   From our PheWAS, there are two further discussion points. The lack of significant associations with

314   other fibrotic/scarring comorbidities (e.g. lung or liver fibrosis) supports previous reports[13,78]

315   although low case numbers may mean our investigations were insufficiently powered to detect them.

316   Secondly, it was striking that all significant associations were positive (i.e. increased prevalence of

317   comorbidities in people with excessive scarring), potentially a result of coverage bias whereby

318   participants with more complete coverage of linked health data may be more likely to have a record

319   of excessive scar diagnosis as well as a diagnosis of any other comorbidity. This may mean that the

320   effect sizes are overestimated, however, the relative order of the associations remains informative.

321   We do not draw causal conclusions from our findings; rather, we inform on co-existing relationships

322   between diseases that may not have previously been appreciated.

13

323   Our inclusion of keloids and hypertrophic scars in the definition of excessive scarring results in a study

324   population that may be heterogeneous with respect to disease severity (and potentially

325   pathophysiology). It might be expected that more severe cases of excessive scarring should be

326   associated with a higher burden of comorbidity. We undertook to formally analyse this by

327   distinguishing a subset of treated excessive scar cases. This attempt to refine the study population to

328   those with moderate-to-severe keloid scarring yielded only 106 individuals, limiting our power to

329   detect statistically significant disease associations and conduct further analyses. This highlights how

330   data availability and information or misclassification bias are key challenges of phenotyping based on

331   EHR. Using currently available clinical codes within UKB, we were only able to establish excessive

332   scarring cases based on potentially subjective clinical assessment without clinicopathological

333   correlation. Nonetheless, our results add to what is already known in the literature, as evidenced by

334   the detection of both previously reported and novel associations.

335   ## Conclusions

336   We report a comprehensive observational analysis of UKB participants with excessive scarring, using a

337   robust modelling approach with adjustments for a variety of disease confounders and associated risk

338   factors. Previously reported disease associations for excessive scarring (hypertension, vitamin D

339   deficiency and atopic eczema) were replicated, but only the association with atopic eczema showed a

340   similar trend across the three major ethnic subgroups (Asian, black and white participants). Our

341   PheWAS implicates a range of unreported associations for reference when studying the

342   pathophysiology of excessive scarring and may prove valuable in studying the associated disease

343   areas.

344

Acknowledgements

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Figure Legend

Figure 1: Multivariate logistic regressions to estimate the effect of excessive scarring status on the risk of each phecode diagnosis, adjusting for age, sex, ethnicity, smoking status, body mass index and Townsend Deprivation Index. Dots represent phecodes and colours represent systemic categories. Statistical significance was set at $p<0.05/1518=3.3\times10^{-5}$ (based on the number of phecodes tested).

Table 1: Baseline characteristics for the scar and comparator groups.

Characteristic	Study Participants[1]	Keloid or Hypertrophic Scar Affected[1]	Keloid or Hypertrophic Scar Unaffected[1]	p-value[2]
Participant numbers	230,078	972	229,106	
Age	64 (8)	63 (8)	64 (8)	**<0.001**
Sex				**<0.001**
Female	125,771 (55%)	633 (65%)	125,138 (55%)	
Male	104,307 (45%)	339 (35%)	103,968 (45%)	
Ethnic Background				**<0.001**
Asian or Asian British	4,707 (2.1%)	53 (5.5%)	4,654 (2.0%)	
Black or Black British	2,509 (1.1%)	61 (6.3%)	2,448 (1.1%)	
Chinese	600 (0.3%)	7 (0.7%)	593 (0.3%)	
Mixed	1,167 (0.5%)	7 (0.7%)	1,160 (0.5%)	
Other ethnic group	1,686 (0.7%)	10 (1.0%)	1,676 (0.7%)	
White	218,331 (95%)	829 (86%)	217,502 (95%)	
Townsend Deprivation Index	-1.33 (3.03)	-1.29 (3.12)	-1.33 (3.03)	0.7
Ever Smoked	135,946 (59%)	526 (54%)	135,420 (59%)	**0.001**
Body Mass Index	27.5 (4.8)	27.9 (5.2)	27.5 (4.8)	0.051
Hypertension	79,034 (34%)	362 (37%)	78,672 (34%)	0.062
Uterine leiomyoma[3]	14,080 (11%)	92 (15%)	13,988 (11%)	**0.009**
Vitamin D deficiency	5,547 (2.4%)	50 (5.1%)	5,497 (2.4%)	**<0.001**
Eczema, atopic	13,501 (5.9%)	99 (10%)	13,402 (5.8%)	**<0.001**

[1]Mean (standard deviation); n (%)
[2]Welch Two Sample t-test; Pearson's Chi-squared test; Statistical significance is declared at P < 0.05 (bold)
[3]Only female participants (N total = 125,771, N affected = 633, N unaffected = 125,138) considered for uterine leiomyoma

Table 2: Associations between excessive scarring and selected
comorbidities.

Outcome	Minimal Model			Full Model		
	OR	95% CI	p-value	OR	95% CI	p-value
Hypertension	1.24	1.08, 1.43	**0.002**	1.11	0.96, 1.30	0.2
Uterine leiomyoma	1.20	0.96, 1.51	0.11	1.19	0.95, 1.49	0.13
Vitamin D deficiency	1.42	1.05, 1.93	0.022	1.47	1.08, 1.99	0.013
Atopic eczema	1.78	1.44, 2.19	**<0.001**	1.68	1.36, 2.07	**<0.001**

OR = Odds Ratio, CI = Confidence Interval

Minimal model adjusts for age, sex (except uterine leiomyoma) and ethnicity for the entire imputed cohort. Full model adjusts for age, sex (except uterine leiomyoma), ethnicity and additional confounders for the entire imputed cohort (see Methods). Models for uterine leiomyoma are restricted to females only without adjusting for sex.

Statistical significance is declared at P < 0.05/4 = 0.0125 (bold). Nominal statistical significance is italicized.

567

568 ## Table 3A. Summary of comorbidities in cases and controls within the three
569 ## main UKB self-reported ethnic groups.

	White participants			Black participants			Asian participants		
Characteristic	Control, N = 217,502	Case, N = 829	p-value[1]	Control, N = 2,448	Case, N = 61	p-value[1]	Control, N = 4,654	Case, N = 53	p-value[1]
Hypertension	74,175 (34%)	290 (35%)	0.6	1,056 (43%)	38 (62%)	**0.004**	1,995 (43%)	23 (43%)	>0.9
Uterine leiomyoma[2]	12,843 (11%)	63 (12%)	0.6	458 (33%)	18 (47%)	0.083	291 (13%)	4 (14%)	>0.9
Vitamin D deficiency	3,866 (1.8%)	20 (2.4%)	0.2	263 (11%)	6 (9.8%)	>0.9	1,041 (22%)	20 (38%)	**0.013**
Eczema, atopic	12,621 (5.8%)	83 (10%)	**<0.001**	144 (5.9%)	7 (11%)	0.12	323 (6.9%)	8 (15%)	**0.042**

[1] Pearson's Chi-squared test; Statistical significance is declared at P < 0.05 (bold).
[2] Only female participants considered for uterine leiomyoma [N control (white) = 119,053, N case (white) = 544; N control (black) = 1,404, N case (black) = 38; N control (Asian) = 2,157, N case (Asian) = 29].

570 ## Table 3B. Fully adjusted model investigating associations between
571 ## excessive scarring and selected comorbidities within the three main UKB
572 ## self-reported ethnic groups.

	White participants			Black participants			Asian participants		
Outcome	OR[1]	95% CI[1]	p-value[2]	OR[1]	95% CI[1]	p-value[2]	OR[1]	95% CI[1]	p-value[2]
Hypertension	1.08	0.92, 1.28	0.3	2.05	1.13, 3.72	*0.019*	0.95	0.48, 1.86	0.9
Uterine leiomyoma[3]	1.07	0.82, 1.39	0.6	1.93	1.00, 3.71	*0.050*	1.04	0.36, 3.01	>0.9
Vitamin D deficiency	1.32	0.85, 2.07	0.2	0.88	0.37, 2.08	0.8	2.24	1.26, 3.97	**0.006**
Atopic eczema	1.68	1.34, 2.12	**<0.001**	1.89	0.83, 4.28	0.13	2.17	1.01, 4.67	*0.048*

[1] OR = Odds Ratio, CI = Confidence Interval
[2] Statistical significance is declared at P < 0.05/4 = 0.0125 (bold). Nominal/borderline significance is italisized.

[3] Model for uterine leiomyoma is restricted to females only without adjusting for sex.

573

Table 4: Phecodes significantly associated with keloid and hypertrophic scar status.

Group	Phecode description
Genitourinary (15)	**Mastodynia**; Hypertrophy of breast (Gynecomastia); Inflammatory disease of breast; Cystitis; Frequency of urination and polyuria; Lump or mass in breast; Irregular menstrual cycle; Excessive or frequent menstruation; Ovarian cyst; Noninflammatory disorders of vagina; Noninflammatory disorders of vulva and perineum; Premenstrual tension syndromes; Urinary tract infection; Renal failure NOS; Inflammatory diseases of uterus, except cervix
Dermatologic (14)	**Sebaceous cyst**; **Diseases of hair and hair follicles**; **Atopic/contact dermatitis due to other or unspecified**; **Other local infections of skin and subcutaneous tissue**; **Seborrheic keratosis**; **Actinic keratosis**; **Acne**; Rash and other nonspecific skin eruption; Other hypertrophic and atrophic conditions of skin; Hyperhidrosis; Disturbance of skin sensation; Carbuncle and furuncle; Pruritus and related conditions; Diseases of nail, NOS
Respiratory (12)	**Acute upper respiratory infections of multiple or unspecified sites**; **Cough**; **Acute sinusitis**; Other diseases of respiratory system, NEC; Acute pharyngitis; Acute laryngitis and tracheitis; Influenza; Shortness of breath; Pneumonia; Pneumonia due to fungus (mycoses); Chronic sinusitis; Chronic pharyngitis and nasopharyngitis
Infectious diseases (11)	**Postoperative infection**; Tuberculosis; Viral warts & HPV; Dermatophytosis of nail; Sexually transmitted infections (not HIV or hepatitis); Dermatophytosis; Candidiasis; Herpes simplex; Viral infection; Mycoses; Gram negative septicemia
Sense organs (11)	**Conjunctivitis, infectious**; Dizziness and giddiness (Light-headedness and vertigo); Inflammation of eyelids; Eustachian tube disorders; Disorders of lacrimal system; Otalgia; Otitis externa; Infection of the eye; Hearing loss; Conjunctivitis, noninfectious; Tinnitus
Neoplasms (8)	**Other non-epithelial cancer of skin**; Melanomas of skin; Malignant neoplasm, other; Lipoma; Other benign neoplasm of connective and other soft tissue; Benign neoplasm of lip, oral cavity, and pharynx; Malignant neoplasm of female breast; Nevus, non-neoplastic
Symptoms (8)	**Malaise and fatigue**; **Back pain**; **Cervicalgia**; Abdominal pain; Nausea and vomiting; Swelling of limb; Sciatica; Edema
Circulatory system (7)	Angina pectoris; Nonspecific chest pain; Other chronic ischemic heart disease, unspecified; Coronary atherosclerosis; Heart valve replaced; Endocarditis; Orthostatic hypotension
Musculoskeletal (7)	**Pain in joint**; **Peripheral enthesopathies and allied syndromes**; **Enthesopathy**; Bursitis; Other and unspecified disc disorder; Other disorders of soft tissues; Juvenile osteochondrosis

Group	Phecode description
Digestive (6)	Hemorrhage of rectum and anus; Symptoms involving digestive system; Irritable Bowel Syndrome; Diseases of lips; Anal and rectal polyp; Dysphagia
Neurological (5)	Acute pain; Organic or persistent insomnia; Other headache syndromes; Other peripheral nerve disorders; Migraine
Injuries & poisonings (3)	Sprains and strains; Contusion; Certain early complications of trauma or procedure
Endocrine/metabolic (2)	Abnormal weight gain; Hypercholesterolemia
Mental disorders (1)	Adjustment reaction

Significant associations with excessive scarring ($p < 0.05/1518 = 3.3 \times 10^{-05}$), grouped by category (number of phecodes per category shown in brackets). The 20 most significantly associated phecodes are in bold.
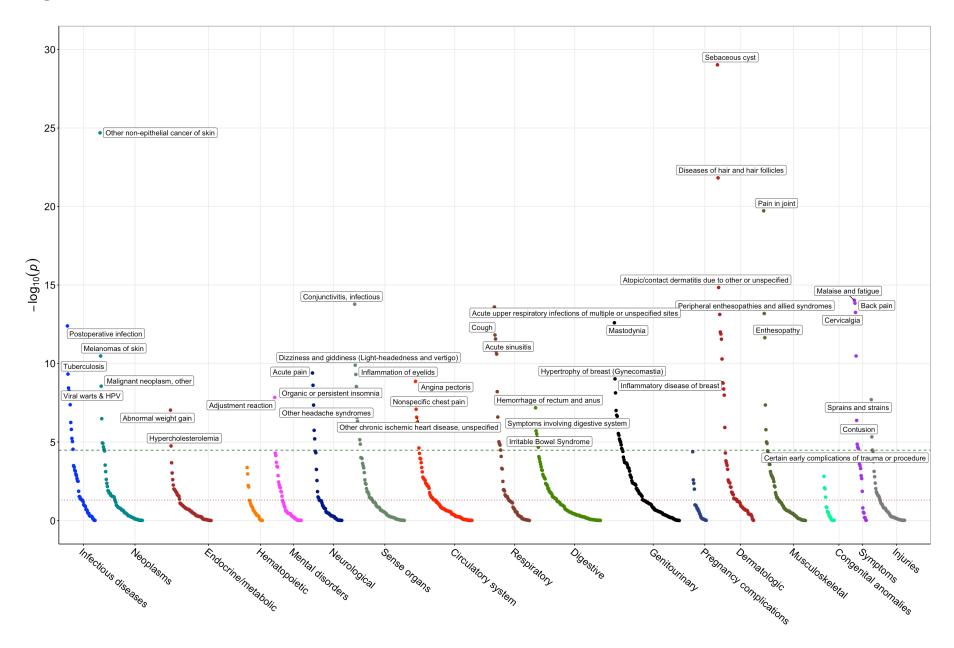
576

Figure 1

Figure 1: Multivariate logistic regressions to estimate the effect of excessive scarring status on the risk of each phecode diagnosis, adjusting for age, sex, ethnicity, smoking status, body mass index and Townsend Deprivation Index. Dots represent phecodes and colours represent systemic categories. Statistical significance was set at P < 0.015/1518 (based on the number of phecodes tested).