

1 **What was known before**

2 DH are an infrequent finding in normal eyes but are common in eyes with NTG.

3 DH are associated with increasing age, vascular disease and female gender.

4 **What this study adds**

5 This is the first UK population based study to report prevalence of DH.

6 This is the first study to report a possible increased prevalence of RPD in eyes with DH and

7 NTG, suggesting a possible shared aetiology of choroidal ischaemia, but further larger

8 studies are required to confirm these findings.

9 **Prevalence of optic disc haemorrhages in an elderly UK Caucasian**
10 **population and possible association with reticular pseudodrusen-**
11 **The Bridlington Eye Assessment Project (BEAP): A Cross-Sectional**
12 **Study (2002-2006).**

13 **Running title: Prevalence of disc haemorrhages in a UK population study**

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43

44 **Abstract**

45 **Aims:** To determine disc haemorrhages (DH) prevalence in an elderly UK population-the
46 Bridlington Eye Assessment Project (BEAP).

47 **Methods:** Thirty-degree (30°) fundus photographs (3549 participants ≥65 years) were
48 graded for DH/macula changes. Glaucoma evaluation included Goldmann tonometry, 26-
49 point suprathreshold visual-fields and mydriatic slit-lamp assessment for glaucomatous
50 optic neuropathy.

51 **Results:** 3548 participants with photographs in at least one eye. DH were present in 53
52 subjects (1.49%), increasing from 1.17% (65-69-year age-group) to 2.19% (80-84-year age-
53 group), $p=0.06$. DH was found in 9/96 (9.38%) right eyes (RE) with open angle glaucoma
54 (OAG). Two of twelve RE (16.67%) with normal tension glaucoma (NTG) had DH. Prevalence
55 in eyes without glaucoma was lower (32/3452, [0.93%]). Reticular pseudodrusen (RPD)
56 occurred in 170/3212 (5.29%) subjects without DH, and 8/131 subjects (6.11%) with OAG.
57 Twenty (20) eyes had normal tension glaucoma (NTG), 2 of whom had RPD (10%) ($p=0.264$).
58 Within a logistic regression model, DH was associated with glaucoma (OR 10.2, 95% CI 5.32 -
59 19.72) and increasing age (OR 1.05, 95% CI 1.00-1.10, $p=0.03$). DH was associated with RPD
60 ($p=0.05$) with univariate analysis but this was not statistically significant in the final adjusted
61 model. There was no significant association with gender, diabetes mellitus (DM),
62 hypertension treatment or AMD grade.

63 **Conclusion:** DH prevalence is 1.5% in those over 65 years old and significantly associated
64 with glaucoma and increasing age. There appears to be increased RPD prevalence in eyes
65 with DH and NTG with age acting as a confounding factor. Larger studies are required to

66 fully assess the relationship and investigate a possible shared aetiology of choroidal
67 ischaemia.

68

69 **Introduction**

70 Optic disc haemorrhages (DH) in association with glaucoma are characteristically flame or
71 splinter shaped, occurring at the border of, or involving the optic nerve head. Originally
72 reported by Bjerrum in 1889, the term 'glaucoma haemorrhagicum' was used to describe
73 patients with glaucoma and DH.¹ They are considered a hallmark for glaucomatous optic
74 neuropathy.²⁻⁹ Approximately 100 years later, Drance and Begg recognised the association
75 between DH and glaucoma progression after noting a patient with 'chronic simple
76 glaucoma' and asymptomatic DH developed a new corresponding visual field (VF) defect
77 with subsequent neuroretinal rim focal thinning.¹⁰ Drance and colleagues later published
78 their finding that 71% of primary open angle glaucoma (POAG) patients with evidence of DH
79 developed progressive VF defects, compared to 33% of those without.² They reported that
80 among patients with ocular hypertension, 34% with a visible DH developed VF defects,
81 compared to 3% of those without.²

82 Several population based studies have published the prevalence of DH, demonstrating they
83 are infrequently found in normal eyes (0.9-3.4%).^{4,11-15} They have their highest prevalence
84 (11-46%) in eyes with normal-tension glaucoma (NTG),^{13,16-18} with lower prevalence among
85 eyes with POAG (2-37%) and OHT (0.4%-10%).^{13,14,17} There are reports DH are more
86 common in women, with increasing age and vascular disease.¹³ Other associations include
87 diabetes mellitus,^{13,19} migraine,¹³ pseudoexfoliation,¹³ aspirin use,¹⁹ and systemic
88 hypertension.^{13,20} Jonas et al reported disc morphology associations. Among POAG patients,

89 those with small neuroretinal rims and large peripapillary beta zone changes were more
90 likely to develop DH.²¹ Hospital-based prevalence studies however, have the disadvantage
91 of selection bias. In the UK no population based study has measured DH prevalence.

92 The purpose of the present study is to report DH prevalence in an elderly UK population,
93 among those with and without glaucoma and investigate associations with systemic and
94 ocular parameters.

95 **Methods**

96 Study Design

97 The Bridlington Eye Assessment Project (BEAP) Study methodology, including image
98 acquisition and analysis are described elsewhere.²² Briefly, the BEAP is a single centre
99 population based prevalence study, designed to investigate the utility of screening for eye
100 disease in an elderly population ≥ 65 years, using clinical examination by optometrists and
101 digital imaging technology. Primary ophthalmic diseases studied were AMD, cataract and
102 glaucoma. Bridlington is a coastal town in Yorkshire, UK, with a stable, predominantly
103 Caucasian population. The study received approval from the local ethics committee
104 (Scarborough and North East Yorkshire Local Ethics Research Committee; Ref No.
105 PB/RH/02/288). Its methodology adhered to the tenets of the Declaration of Helsinki. Study
106 recruitment occurred between 5/11/2002 and 29/03/2006. All participants were
107 interviewed, in person, by a trained research nurse using a structured questionnaire, and
108 examined by one of four specially trained optometrists with a pro-forma completed by
109 research staff. Non-stereoscopic mydriatic fundus photography was performed with a
110 Topcon fundus camera (model TRC NW6S) and Nikon 10-megapixel camera. Each eye had a
111 30⁰ colour fundus photograph taken (CFP), centred on the macula. In total 3549 individuals

112 attended the initial study examination (56% of the eligible population). Basic demographic
113 information was available for all subjects within the sampling frame. Gender balance was
114 similar for both attenders and non-attenders.

115 Two ophthalmologists (CW and RN) independently examined each photograph for the
116 presence of DH. All CFP were separately graded for other ocular pathologies including AMD
117 and reticular pseudodrusen (RPD) by one examiner (CW) using definitions and grids as
118 described in the International Classification System for AMD and as reported elsewhere.²²

119 Grading was masked, in the absence of all demographic data, and results of ocular
120 examinations, tests or final diagnoses. Each eye was graded separately. The final grade
121 assigned to each participant was that of either eye.

122 DH were defined as haemorrhages lying completely inside the optic nerve head, those
123 extending beyond, or those touching the optic disc border. Examples are shown in Figures 1
124 and 2. Haemorrhages located completely outside the optic disc head were excluded, as they
125 may be secondary to other ocular diseases. Eyes with visible diabetic retinopathy, retinal
126 vein occlusions or collateral disc vessels, optic disc oedema or eyes with signs of other
127 ocular pathology, such as peripapillary choroidal neovascular membranes, were excluded
128 from analysis. In eyes with DH the number, locations and shapes were recorded.

129 All photographs showing DH were reviewed by a glaucoma subspecialist (SAV) who acted as
130 final arbiter.

131 Within the BEAP all subjects were assessed for glaucoma. Intraocular pressure (IOP) was
132 measured using a calibrated Goldmann applanation tonometer. Visual field testing using a
133 Henson Pro 5000 automated perimeter, software v3.1.4 (Tinsley Instruments, Croydon, UK)

134 with single-stimulus, suprathereshold, central 26-point strategy was employed. The test was
135 automatically extended to 68-points if defects were detected. The perimeter automatically
136 graded outputs as normal, suspect or defect. For study purposes, any defect including those
137 classified as suspicious were treated as abnormal. Estimation of vertical cup to disc ratio
138 was performed using a 90D condensing lens by the examining optometrist, who recorded
139 the presence of pathological features, including DH, bayonetting and focal notching, before
140 deciding if the disc appeared abnormal using criteria developed by Jonas et al.^{23, 24} Subjects
141 with abnormal visual fields, raised IOP (≥ 21 mmHg), or disc features suspicious for glaucoma
142 were referred to the hospital eye service (HES) for assessment by one of four consultant
143 ophthalmologists. A definitive clinical diagnosis of glaucoma would be assigned following
144 clinic assessment or appropriate follow up. All glaucoma diagnoses were reviewed by a
145 single glaucoma subspecialist (SAV) using a minimum of 5 years longitudinal data to
146 confirm incident disease at referral.

147 Statistical Methods

148 All data was analysed with Stata v14 (Stata Corp, College Station, Tx, USA). Associations
149 between groups were explored using unpaired t-tests for continuous variables and chi
150 squared test for discrete variables. Where necessary, results were stratified using Mantel
151 Haenzel methods. Logistic regression was used for multivariate analysis and to determine
152 odd ratios in the final adjusted model and was computed using a step wise approach with
153 each relevant additional variable added sequentially and the model re-checked for change.

154

155 **Results**

156 In total, 3548 Caucasian participants had gradable photographs of the optic nerve in at least
157 one eye, with 3255 having gradable CFP in both. DH were present in 53 subjects (1.49%
158 prevalence for either eye), in the ≥ 65 -year age group. A total of 25 subjects with DH were
159 female (47.2%). Males had a higher gender specific prevalence (1.79% vs 1.26%) ($p=0.19$);
160 on multivariate logistical regression analysis this difference was not statistically significant
161 (OR female gender 0.65, CI 0.37-1.14). DH frequency for right ($n=41$, 77.4%) and left eyes
162 ($n=12$, 22.6%) appeared to be different. Mean age for subjects with DH was 77.01 years (SD
163 7.55 [Table 1]) and DH prevalence demonstrated a trend to increase with age from 1.17% in
164 the 65-69-year age-group, to a maximum of 2.19% in the 80-84-year age-group ($p=0.06$).

165 For right eyes, 32 out of 41 (78.0%) DH occurred in eyes without a definite diagnosis of OAG.

166 In total, 96 of 3548 right eyes (2.7%) had open angle glaucoma (OAG). Of all 41 right eyes
167 with DH, 9 had definite OAG glaucoma (22%), representing 9 out of 96 (9.38%) DH right eyes
168 with definite OAG. Twelve (12) right eyes were identified with normal tension glaucoma
169 (NTG), of which 2 had DH (16.67%). The prevalence of DH in non-glaucomatous eyes was
170 0.93% (32 of 3452 eyes). In a univariate analysis, presence of DH was significantly ($P<0.05$)
171 associated with older age and NTG.

172 RPD occurred in 170 of 3212 (5.29%) subjects with no DH, and in 8 of 131 subjects (6.11%)
173 with OAG. Twenty (20) eyes had NTG, 2 of which had RPD (10%) ($p=0.264$). In univariate
174 analysis, DH were significantly associated with the presence of RPD ($p=0.048$). Among the
175 3264 subjects with gradable images (for both RPD and DH), 6 of 52 eyes (11.54%) with DH
176 had RPD. 5 of 53 eyes (9.43%) with DH had either geographic atrophy or neovascular AMD
177 in their worse eye.

178 Within a logistic regression model, we found that DH was associated with glaucoma (OR
179 10.2, 95% CI 5.32 - 19.72) and increasing age (OR 1.05, 95% CI 1.00-1.10, $p=0.03$)
180 corresponding to annual 5% increase in risk. DH was associated with RPD ($p=0.05$) in the
181 univariate analysis but this was not significant in the final adjusted model. There was a weak
182 association between RPD and DH ($p=0.05$) which was not significant when we corrected for
183 age (OR 1.87, CI 0.74-4.74, $p=0.18$). There was no significant association between DH and
184 gender, diabetes mellitus (DM), hypertension treatment or AMD grade.

185 **Discussion**

186 Despite their importance and association with glaucoma, no UK population based report of
187 DH prevalence exists, with a paucity of studies from European Caucasian populations. Many
188 reports are hospital based focusing on subjects with an established glaucoma diagnosis,
189 ocular hypertension or documented DH, with associated selection bias.^{3,4,13,25,26} The
190 prevalence of DH in the Bridlington (UK) population (aged ≥ 65 years) of 1.5% is comparable
191 to that in other large population based studies, including 1.2% in Japan,¹⁴ Australia (1.4%),¹³
192 United States (0.9%)¹¹ and China (1.2%).¹² To date our finding represents the highest
193 population based prevalence which may reflect the older age of our cohort.

194 In this study, DH was significantly associated with age, with prevalence reaching 2.19% in
195 the 80-84 year age group. This is consistent with previous population¹² and hospital based
196 studies.^{21,27} Jonas et al reported an odds ratio of 1.48 for 10-year increase in age for DH
197 development.²¹ In the Ocular Hypertension Treatment Study (OHTS), patients with DH were
198 older than those without (59.0 vs 55.2 years, $p<0.01$).²⁷ Our finding of a 1.05 increased risk
199 of DH per year is similar to that in the Korean National Health and Nutritional Examination
200 Survey (1.04 fold increased risk per year).²⁸

201 Previous studies have reported conflicting results relating to the association between DH
202 and gender. In this study, DH prevalence was higher in men but the difference was not
203 statistically significant (OR female gender 0.65, CI 0.37-1.14). This is in line with population
204 based studies from South Korea²⁹ and China.¹² In the Blue Mountains Eye Study (BMES), DH
205 prevalence was higher in woman (OR 1.9, CI 1.0-3.5),¹³ after adjustment for age and
206 glaucoma, while a female preponderance has also been reported elsewhere.^{11,30,31}

207 This study confirms most DH occur in healthy individuals with no (current) diagnosis of
208 glaucoma, while only 27% of DH occur in glaucomatous eyes (OAG or NTG), reflecting the
209 relative rarity of OAG. This finding is higher than in the Beijing Eye Study (where 20% of DH
210 was detected in glaucomatous eyes).¹²

211 Glaucoma remains the most important disease associated with DH and the reported
212 prevalence among glaucoma patients varies considerably, ranging from 4.2% to 17.6% for
213 primary open angle glaucoma and 19.4% and 35.3% for NTG.^{13,16,32-34} In our study DH
214 prevalence in subjects with OAG was 9.4%, being similar to other population based reports,
215 including 13.8% in the BMES, 8.8% in the Beijing Eye Study and 8.2% in the Tajimi study.³¹
216 Our findings of higher DH prevalence among eyes with NTG (16.7%) is in keeping with
217 previously published reports.¹³

218 The positive predictive value (PPV) of DH varies throughout the literature, appearing to
219 reflect the type of glaucoma most prevalent within the population. In a Japanese study,
220 where NTG is most prevalent, the PPV was high (52.9%).¹⁴ Of clinical relevance is the finding
221 that a DH in our UK population has a PPV of 27% for OAG or NTG, as 27% of right eye DH's
222 were found in eyes with OAG or NTG. This is similar to findings from other studies within
223 predominantly Caucasian populations of European ancestry.¹³

224 The putative finding of higher DH frequency for right eyes (n=41, 77.4% vs n=12, 22.6%) was
225 unexpected, likely reflecting a chance finding. Laterality of DH is often not reported or
226 discussed. The unit of study is often either eye. In the BMES,¹³ DH prevalence was highest
227 for left eyes (34/56, 60.7% vs 22/56, 39.3%). Siegner et al⁸ in a hospital based population
228 reported DH were identified in 51% of right eyes. It has been demonstrated that low
229 diastolic perfusion pressure (DPP) is an independent risk factor for development OAG,³⁵
230 with suggestions that lower ocular perfusion pressure results in reduced ocular blood
231 supply, resulting in glaucomatous optic neuropathy. Differences in systolic BP between arms
232 can predict increased risk of cardiovascular events and all-cause mortality over a ten-year
233 period in people with hypertension.³⁶ Some studies have suggested that diastolic BP is, on
234 average, lower in the right arm and may be related to differing pulse pressures along the
235 aorta.³⁶⁻³⁸ However, the literature is inconsistent and inconclusive.

236 The pathogenesis of DH has not been fully elucidated. We report a newly described ocular
237 association between DH and RPD, which may offer further insight into DH aetiology. We
238 draw comparisons between demographic and pathological similarities among subjects with
239 RPD, DH and NTG, and propose they may share an aetiological connection through choroidal
240 ischaemia.

241 Within the BEAP, RPD are more common than recognized in prior population based studies,
242 with a prevalence of 5% in persons aged ≥ 65 years. Like NTG, RPD are consistently more
243 prevalent in females. Their prevalence, like NTG, increases significantly with age, reaching a
244 maximum of 27% in persons aged ≥ 90 years.²² In the current study RPD prevalence is
245 increased in individuals with NTG (11.5%) when compared to the population as a whole
246 (5%), or when compared to all subjects with OAG (6.11%); in a univariate model, DH were

247 associated with RPD ($p=0.048$), although this association was lost in multivariate analysis.
248 Given the relative rarity of DH and RPD, and small numbers involved (with age acting as a
249 confounding factor), a larger sample size may be required to confirm or refute any genuine
250 association.

251 Arnold et al speculated that RPD result from poor choroidal perfusion after describing
252 fibrosis within choroidal stroma between large choroidal veins.³⁹ While choroidal thinning is
253 consistently found in eyes with RPD,^{40,41} juxtapapillary choroidal thinning has been
254 documented in eyes with NTG.⁴²⁻⁴⁴ Others have demonstrated reduced blood flow in the
255 peripapillary retina in NTG eyes,^{45,46} suggesting blood flow deficits may accompany or
256 contribute to NTG. RPD may form part of a spectrum of chorioretinal changes seen in age-
257 related choroidal atrophy (ACA), in which peripapillary atrophy (PPA), tessellation of the
258 fundus, choroidal thinning and glaucoma are described associations.⁴⁷ There is increasing
259 evidence of an association between RPD and cardiovascular disease and risk factors,
260 including hypertension⁴⁸ and angina.⁴⁹ A recent publication demonstrated an association
261 with diffuse-trickling GA (which is strongly associated with RPD) and cardiovascular disease,
262 particularly in males,⁵⁰ and in the < 65-years age-group, 54% of patients had previously been
263 admitted to hospital with cardiovascular disease, including hypertensive crisis, angina and
264 myocardial infarction.⁵⁰ Similar associations between vascular insufficiency and NTG have
265 been raised. Migraines are associated with transient vasospastic episodes that can result in
266 impaired cerebral blood flow and have been consistently associated with NTG^{51,52} and
267 progression of NTG.⁵³ In the Low-Pressure Glaucoma Treatment Study a history of migraine,
268 low systolic blood pressure and use of systemic β blockers were associated with DH.⁵⁴
269 Hypertension, like RPD, has also been associated with DH in NTG.²⁰

270 PPA is another known feature shared among subjects with NTG (often with cupping most
271 pronounced in areas of RPE loss),⁵⁵ DH⁵⁶ and RPD,⁵⁷ offering further biological plausibility
272 into a shared common pathway. Interestingly, flame shaped DH occur most frequently in a
273 superotemporal location.¹³ Similarly, RPD have increased prevalence within the
274 superotemporal macula.⁵⁸ We hypothesise that RPD, DH and NTG, in some instances, may
275 be manifestations of the same aetiological pathway of choroidal ischaemia. We highlight the
276 short posterior ciliary arteries (SPCA) supply both the choroid and prelaminar portion of the
277 optic nerve head, along with the peripapillary choroid. We hypothesise chronic ischaemia
278 via the SPCA may result in a spectrum of overlapping changes including DH, PPA, RPD and
279 NTG in some individuals. Large prospective studies in NTG patients are required to
280 investigate this association further. Utilisation of multimodal imaging for the optic disc,
281 peripapillary area and macula choroid, with perfusion studies would be invaluable.

282 The possible association of RPD and NTG is important. The Beaver Dam Eye Study (BDES)
283 reported not only an association between RPD and glaucoma, but the highest 15-year
284 incidence of AMD among subjects with RPD (43% and 46% in right and left eyes
285 respectively).⁵⁸ This was twice the risk when compared to subjects with soft indistinct
286 drusen. If RPD, DH and NTG are associated through shared aetiological mechanisms,
287 patients with NTG will need appropriate macula imaging in clinics, advice regarding risk of
288 AMD with provision of lifestyle advice and amsler grid for home screening. Similarly,
289 clinicians should have a high index of suspicion while reviewing patients with RPD, paying
290 attention to optic disc morphology for features of NTG, being aware of potential difficulties
291 in diagnosing NTG in patients with AMD. Moreover, there is evidence suggesting patients
292 with AMD and glaucoma pose extra hazards such as increased difficulties walking safely

293 when compared to patients with glaucoma alone.⁵⁹ This is not surprising when glaucoma
294 predominantly affects tasks requiring contrast discrimination and peripheral vision/light-
295 dark adaptation,⁶⁰ while AMD influences tasks involving central vision such as reading and
296 recognizing faces.⁶¹

297 Limitations of this study include its purely Caucasian participants, which could limit
298 generalizability to the wider UK population. Optic disc and macula imaging was limited to
299 non-stereoscopic colour fundus photographs. Multimodal imaging would have been
300 preferred for both, particularly for detecting RPD. Prospective follow up would have been
301 preferred. While we have corrected for the majority of important co-variants, there are
302 known associations that were not specifically questioned such as a history of Raynaud's
303 phenomenon, migraines and use of β blockers or anti-coagulants.

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459

460 **Figure Legends**

461 **Figure 1:** Colour fundus photograph of right eye showing extensive dot and ribbon RPD.
462 There is an inferior DH with associated thinning of the neuroretinal rim and a focal notch.
463 There is temporal bayoneting at the optic disc edge. There is a tessellated appearance to
464 the fundus with decreased pigmentation inferior to the optic disc and peripapillary
465 pigmentary changes. There are sparsely visible choroidal vessels between the optic disc
466 and macula.

467 **Figure 2:** Superonasal neuroretinal rim DH associated with co-morbid geographic
468 atrophy and temporal ribbon RPD. There are some photographic features of age related
469 choroidal atrophy including peripapillary atrophy and pigmentary changes. There is a
470 large area of inferior scleral show.

471

472

Table 1. The characteristics of patients with and without disc haemorrhages (DH). Data is: number (percentage) unless otherwise stated.

Variable		With DH	Without DH	Total	p-value t-test * Chi ² #
Mean age [years] (95% Confidence Interval)		77.01 (74.93-79.09)	75.04 (74.84-75.23)	75.07 (74.87-75.26)	0.016*
Gender	Male	28 (1.80)	1530 (98.20)	1558	0.195 #
	Female	25 (1.26)	1953 (98.74)	1978	
Diabetes Mellitus	Yes	3 (0.85)	352 (99.15)	355	0.283 #
	No	50 (1.58)	3121 (98.42)	3171	
Hypertension treatment	Yes	27 (1.60)	1662 (98.40)	1689	0.701 #
	No	26 (1.44)	1780 (98.56)	1806	
Patients with no AMD in worse eye (Rotterdam grade 0)	Yes (Grade 0)	20 (1.5)	1317 (98.50)	1337	0.991 #
	No (Grade 1-4)	33 (1.50)	2166 (98.50)	2199	



