

Appendix A.

Table A1. Associations between patient characteristics and two week wait referrals received within two weeks of visiting the GP (sensitivity analysis considering only referrals flagged as “two week wait”). This table was created by the authors.

| | Unadjusted odds ratio | Lower 95% confidence interval | Upper 95% confidence interval | P | Odds ratio | Lower 95% confidence interval | Upper 95% confidence interval | P |
|----------------------------|-----------------------|-------------------------------|-------------------------------|--------|------------|-------------------------------|-------------------------------|--------|
| <i>Features</i> | | | | | | | | |
| Anaemia | 1.35 | 1.12 | 1.62 | <0.001 | 1.28 | 1.06 | 1.54 | <0.001 |
| Rectal bleeding | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | |
| Dysphagia | 1.12 | 1.02 | 1.23 | | 1.24 | 1.13 | 1.36 | |
| Breast lump | 12.91 | 11.98 | 13.90 | | 18.05 | 16.43 | 19.83 | |
| Haematuria | 2.97 | 2.72 | 3.25 | | 2.94 | 2.68 | 3.23 | |
| Post-menopausal bleeding | 9.69 | 8.74 | 10.75 | | 10.30 | 9.22 | 11.51 | |
| <i>Age</i> | | | | | | | | |
| 18 to 24 years | 0.06 | 0.02 | 0.16 | <0.001 | 0.14 | 0.05 | 0.38 | <0.001 |
| 25 to 34 years | 1.36 | 1.21 | 1.53 | | 0.36 | 0.32 | 0.42 | |
| 35 to 44 years | 2.33 | 2.15 | 2.53 | | 0.62 | 0.56 | 0.69 | |
| 45 to 54 years | 1.52 | 1.42 | 1.63 | | 0.83 | 0.76 | 0.90 | |
| 55 to 64 years | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | |
| 65 to 74 years | 0.92 | 0.85 | 0.99 | | 1.18 | 1.08 | 1.28 | |
| 75 to 84 years | 0.83 | 0.77 | 0.90 | | 1.24 | 1.13 | 1.37 | |
| 85 or older | 0.68 | 0.61 | 0.76 | | 1.05 | 0.92 | 1.20 | |
| Sex (Female) | 3.32 | 3.13 | 3.52 | <0.001 | 1.00 | 0.93 | 1.08 | 1.000 |
| <i>IMD</i> | | | | | | | | |
| 1 (least deprived) | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.744 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.122 |
| 2 | 0.97 | 0.91 | 1.04 | | 0.99 | 0.91 | 1.07 | |
| 3 | 0.95 | 0.88 | 1.03 | | 0.93 | 0.86 | 1.02 | |
| 4 | 0.98 | 0.90 | 1.07 | | 1.05 | 0.96 | 1.16 | |
| 5 (most deprived) | 0.96 | 0.87 | 1.06 | | 0.97 | 0.87 | 1.09 | |
| <i>Comorbidities</i> | | | | | | | | |
| 0 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | <0.001 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.008 |
| 1 | 0.88 | 0.82 | 0.94 | | 0.97 | 0.90 | 1.05 | |
| 2 | 0.81 | 0.75 | 0.86 | | 0.92 | 0.85 | 1.00 | |
| 3 | 0.72 | 0.67 | 0.78 | | 0.88 | 0.80 | 0.96 | |
| 4 or more | 0.60 | 0.56 | 0.65 | | 0.87 | 0.79 | 0.96 | |
| Previous history of cancer | - | - | - | | 0.89 | 0.80 | 0.99 | 0.030 |

Table A2. Associations between patient characteristics (including ethnicity) and urgent referrals received within two weeks after visiting the GP (sensitivity analysis including adjustment for ethnicity). This table was created by the authors.

| | Unadjusted odds ratio | Lower 95% confidence interval | Upper 95% confidence interval | P | Odds ratio | Lower 95% confidence interval | Upper 95% confidence interval | P |
|--------------------------|-----------------------|-------------------------------|-------------------------------|--------|------------|-------------------------------|-------------------------------|--------|
| <i>Features</i> | | | | | | | | |
| Anaemia | 1.17 | 1.01 | 1.37 | <0.001 | 0.91 | 0.77 | 1.08 | <0.001 |
| Rectal bleeding | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | |
| Dysphagia | 0.91 | 0.84 | 0.99 | | 0.97 | 0.88 | 1.06 | |
| Breast lump | 12.15 | 11.41 | 12.94 | | 14.77 | 13.36 | 16.33 | |
| Haematuria | 3.29 | 3.05 | 3.54 | | 2.75 | 2.52 | 3.01 | |
| Post-menopausal bleeding | 9.57 | 8.74 | 10.48 | | 8.80 | 7.79 | 9.95 | |
| <i>Age</i> | | | | | | | | |
| 18 to 24 years | 0.08 | 0.04 | 0.16 | <0.001 | 0.20 | 0.08 | 0.52 | <0.001 |
| 25 to 34 years | 1.41 | 1.28 | 1.56 | | 0.37 | 0.31 | 0.43 | |
| 35 to 44 years | 2.25 | 2.10 | 2.42 | | 0.60 | 0.53 | 0.68 | |
| 45 to 54 years | 1.47 | 1.39 | 1.56 | | 0.82 | 0.75 | 0.90 | |
| 55 to 64 years | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | |
| 65 to 74 years | 0.90 | 0.84 | 0.96 | | 1.03 | 0.94 | 1.12 | |
| 75 to 84 years | 0.83 | 0.78 | 0.89 | | 1.06 | 0.97 | 1.17 | |
| 85 or older | 0.64 | 0.58 | 0.71 | | 1.00 | 0.88 | 1.13 | |
| Sex (Female) | 3.06 | 2.92 | 3.21 | <0.001 | 1.03 | 0.96 | 1.11 | 0.409 |
| <i>IMD</i> | | | | | | | | |
| 1 (least deprived) | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.775 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.792 |
| 2 | 0.98 | 0.93 | 1.05 | | 0.95 | 0.87 | 1.04 | |
| 3 | 1.03 | 0.96 | 1.10 | | 0.96 | 0.88 | 1.06 | |
| 4 | 1.00 | 0.93 | 1.08 | | 0.99 | 0.90 | 1.10 | |
| 5 (most deprived) | 1.00 | 0.92 | 1.08 | | 0.95 | 0.85 | 1.07 | |
| <i>Comorbidities</i> | | | | | | | | |
| 0 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | <0.001 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | <0.001 |
| 1 | 0.90 | 0.85 | 0.95 | | 0.95 | 0.87 | 1.04 | |
| 2 | 0.85 | 0.80 | 0.90 | | 0.88 | 0.80 | 0.96 | |
| 3 | 0.74 | 0.69 | 0.79 | | 0.76 | 0.69 | 0.83 | |
| 4 or more | 0.60 | 0.56 | 0.64 | | 0.69 | 0.63 | 0.77 | |
| <i>Ethnicity</i> | | | | | | | | |
| White | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.180 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.864 |
| Black | 1.10 | 0.91 | 1.33 | | 0.93 | 0.75 | 1.16 | |
| Asian | 0.89 | 0.77 | 1.03 | | 0.95 | 0.80 | 1.11 | |
| Mixed | 1.20 | 0.87 | 1.64 | | 0.88 | 0.62 | 1.26 | |

| | | | | | | | | |
|----------------------------|------|------|------|---|------|------|------|-------|
| Other | 1.14 | 0.92 | 1.43 | | 1.02 | 0.80 | 1.31 | |
| Previous history of cancer | - | - | - | - | 0.85 | 0.76 | 0.95 | 0.004 |

Table A3. Associations between patient characteristics and urgent referrals received within 90 days of visiting the GP (sensitivity analysis considering referrals made up to 90 days after presentations rather than up to 14 days as in the main analysis). This table was created by the authors.

| | Unadjusted odds ratio | Lower 95% confidence interval | Upper 95% confidence interval | P | Odds ratio | Lower 95% confidence interval | Upper 95% confidence interval | P |
|--------------------------|-----------------------|-------------------------------|-------------------------------|--------|------------|-------------------------------|-------------------------------|--------|
| <i>Features</i> | | | | | | | | |
| Anaemia | 1.49 | 1.30 | 1.71 | <0.001 | 1.43 | 1.25 | 1.64 | <0.001 |
| Rectal bleeding | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | |
| Dysphagia | 0.90 | 0.84 | 0.97 | | 0.99 | 0.92 | 1.07 | |
| Breast lump | 10.43 | 9.83 | 11.07 | | 14.02 | 12.99 | 15.14 | |
| Haematuria | 2.32 | 2.16 | 2.48 | | 2.31 | 2.15 | 2.48 | |
| Post-menopausal bleeding | 8.72 | 7.97 | 9.54 | | 9.03 | 8.21 | 9.94 | |
| <i>Age</i> | | | | | | | | |
| 18 to 24 years | 0.07 | 0.04 | 0.14 | <0.001 | 0.17 | 0.09 | 0.34 | <0.001 |
| 25 to 34 years | 1.51 | 1.37 | 1.67 | | 0.42 | 0.37 | 0.47 | |
| 35 to 44 years | 2.31 | 2.15 | 2.48 | | 0.62 | 0.57 | 0.68 | |
| 45 to 54 years | 1.42 | 1.34 | 1.50 | | 0.80 | 0.74 | 0.85 | |
| 55 to 64 years | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | |
| 65 to 74 years | 0.91 | 0.85 | 0.96 | | 1.11 | 1.04 | 1.19 | |
| 75 to 84 years | 0.87 | 0.81 | 0.93 | | 1.23 | 1.14 | 1.33 | |
| 85 or older | 0.65 | 0.59 | 0.71 | | 0.93 | 0.84 | 1.03 | |
| Sex (Female) | 3.01 | 2.87 | 3.15 | <0.001 | 1.04 | 0.98 | 1.10 | 0.218 |
| <i>IMD</i> | | | | | | | | |
| 1 (least deprived) | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.578 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.138 |
| 2 | 0.98 | 0.92 | 1.04 | | 1.00 | 0.93 | 1.07 | |
| 3 | 1.03 | 0.96 | 1.10 | | 1.05 | 0.97 | 1.13 | |
| 4 | 1.02 | 0.95 | 1.09 | | 1.09 | 1.01 | 1.18 | |
| 5 (most deprived) | 1.02 | 0.94 | 1.10 | | 1.07 | 0.98 | 1.18 | |
| <i>Comorbidities</i> | | | | | | | | |
| 0 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | <0.001 | <i>Ref</i> | <i>Ref</i> | <i>Ref</i> | 0.026 |
| 1 | 0.90 | 0.85 | 0.95 | | 0.99 | 0.92 | 1.06 | |
| 2 | 0.86 | 0.81 | 0.91 | | 0.99 | 0.93 | 1.06 | |

| | | | | | | | |
|----------------------------|------|------|------|------|------|------|-------|
| 3 | 0.76 | 0.71 | 0.81 | 0.91 | 0.85 | 0.98 | |
| 4 or more | 0.64 | 0.60 | 0.68 | 0.91 | 0.84 | 0.99 | |
| Previous history of cancer | - | - | - | 0.91 | 0.83 | 1.00 | 0.047 |

Table A4. Urgent referral within two weeks of first presentation as captured by either HES or CPRD (sensitivity analysis considering urgent referrals recorded in either CPRD or HES). This table was created by the authors.

| Symptom | No urgent referral in HES (%) | Urgent referral in HES (%) | No urgent referral in CPRD and HES (%) | Urgent referral in CPRD and HES (%) |
|---|-------------------------------|----------------------------|--|-------------------------------------|
| | Main analysis using HES data | | Sensitivity analysis using HES and CPRD data | |
| | N (%) | N (%) | N (%) | N (%) |
| Anaemia (n=1268) | 1007 (79.4%) | 261 (20.6%) | 939 (74.1%) | 329 (26.0%) |
| Rectal bleeding (n=13067) | 10752 (82.3%) | 2315 (17.7%) | 10168 (77.8%) | 2899 (22.2%) |
| Dysphagia (n=8197) | 6813 (83.1%) | 1384 (16.9%) | 5431 (66.3%) | 2766 (33.7%) |
| Breast lump (n=16118) | 5111 (31.7%) | 11007 (68.3%) | 4471 (27.7%) | 11647 (72.3%) |
| Haematuria (n=6604) | 4043 (61.9%) | 2486 (38.1%) | 3507 (53.1%) | 3097 (46.9%) |
| PMB (n=3536) | 1319 (37.3%) | 2217 (62.7%) | 1101 (31.1%) | 2435 (68.9%) |
| Total (n=48715 for HES; n=48790 for CPRD and HES) | 29045 (59.6%) | 19670 (40.4%) | 25617 (52.5%) | 23173 (47.5%) |

Table A5. Urgent referrals for patients diagnosed with cancer. This table was created by the authors.

| Features | Patients with neoplasms excluding neoplasms in situ ¹ | |
|----------------------------------|--|-----------------|
| | No urgent referral | Urgent referral |
| | N (%) | N (%) |
| Anaemia (n=158) | 96 (60.8%) | 62 (39.2%) |
| Rectal bleeding (n=499) | 299 (59.9%) | 200 (40.1%) |
| Dysphagia (n=296) | 209 (70.6%) | 87 (29.4%) |
| Breast lump (n=1353) | 191 (14.1%) | 1162 (85.9%) |
| Haematuria (n=468) | 200 (42.7%) | 268 (57.3%) |
| Post-menopausal bleeding (n=223) | 52 (23.3%) | 171 (76.7%) |

¹ICD-10-CM C codes excluding C44

Table A6. Cancer incidence in patients with and without urgent referral as captured by either HES or CPRD (sensitivity analysis considering urgent referrals recorded in either CPRD or HES). This table was created by the authors.

| Symptom | Cancer incidence | |
|-----------------|---|--------------------------------------|
| | No urgent referral in CPRD and HES (%*) | Urgent referral in CPRD and HES (%*) |
| Anaemia | 79 (8.4%) | 79 (24.0%) |
| Rectal bleeding | 277 (2.7%) | 222 (7.7%) |
| Dysphagia | 140 (2.6%) | 156 (5.6%) |
| Breast lump | 134 (3.0%) | 1,219 (10.5%) |
| Haematuria | 153 (4.4%) | 320 (10.3%) |
| PMB | 39 (3.5%) | 184 (7.6%) |
| Total | 822 (3.2%) | 2,180 (9.4%) |

* Percentage of cancer diagnoses compared to the number of patients who received or did not receive an urgent referral

Table A7. Cancer and neoplasms in situ incidence in patients who did not receive an urgent referral (sensitivity analysis including neoplasms in situ). This table was created by the authors.

| Features | No cancer diagnosis | Cancer diagnosis |
|-----------------------------------|---------------------|------------------|
| | N (%) | N (%) |
| Anaemia (n=1007) | 904 (89.8%) | 103 (10.2%) |
| Rectal bleeding (n= 10752) | 10417 (96.9%) | 335 (3.1%) |
| Dysphagia (n= 6813) | 6591 (96.7%) | 222 (3.3%) |
| Breast lump (n=5111) | 4906 (96.0%) | 205 (4.0%) |
| Haematuria (n=4043) | 3751 (92.8%) | 292 (7.2%) |
| Post-menopausal bleeding (n=1319) | 1264 (95.8%) | 55 (4.2%) |

Table A8. Urgent referrals for patients diagnosed with neoplasms, including neoplasms in situ. This table was created by the authors.

| Features | Patients with neoplasms including neoplasms in situ ¹ | |
|----------------------------------|--|-----------------|
| | No urgent referral | Urgent referral |
| | N (%) | N (%) |
| Anaemia (n=166) | 103 (62.1%) | 63 (38.0%) |
| Rectal bleeding (n=557) | 335 (60.1%) | 222 (39.9%) |
| Dysphagia (n=310) | 222 (71.6%) | 88 (28.4%) |
| Breast lump (n=1425) | 205 (14.4%) | 1220 (85.6%) |
| Haematuria (n=721) | 292 (40.4%) | 430 (59.6%) |
| Post-menopausal bleeding (n=229) | 55 (24.0%) | 174 (76.0%) |

¹ICD-10-CM C and D codes excluding C44

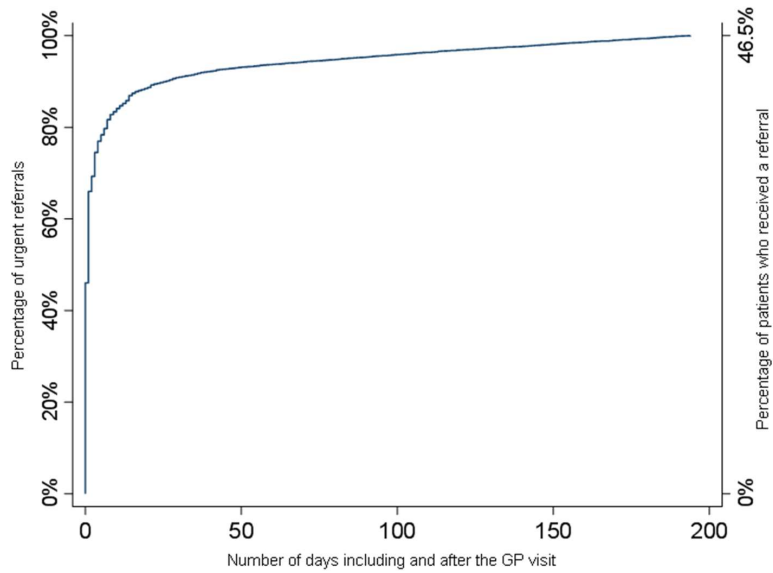


Figure A1. Cumulating urgent referrals within six months of the GP index visit. This figure was created by the authors.

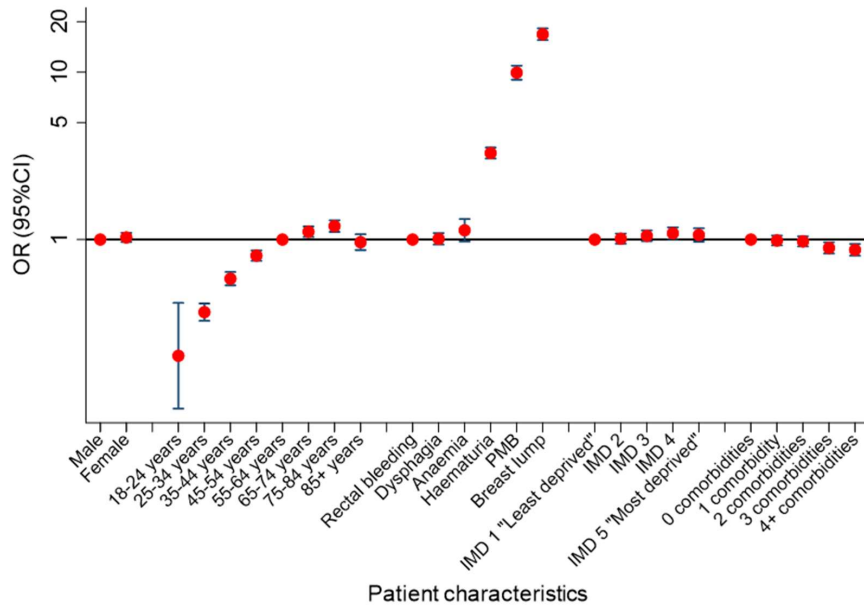
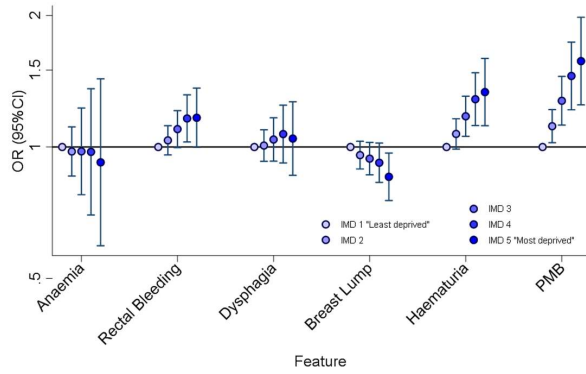
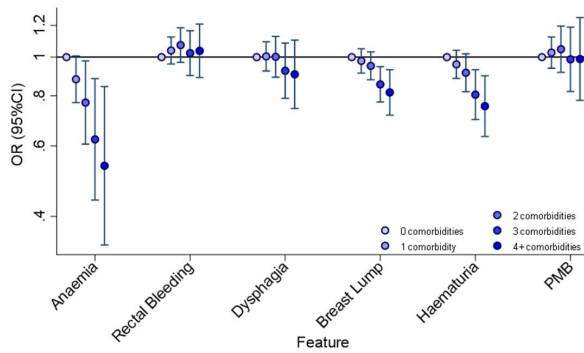


Figure A2. Associations between patient characteristics and receiving an urgent referral within two weeks of visiting the GP. This figure was created by the authors.

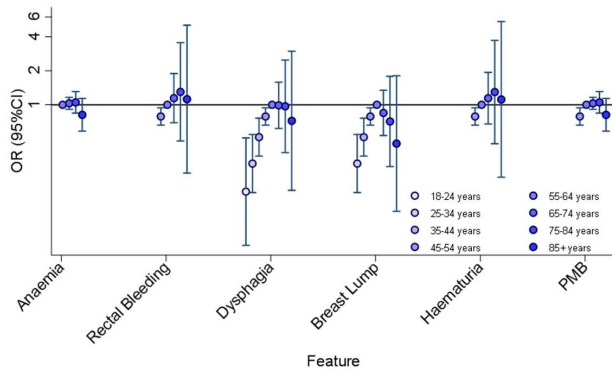
Figure A3: Associations between patient characteristics ((a) deprivation; (b) comorbidities; (c) age) and receiving an urgent suspected cancer referral within two weeks of visiting the GP. This figure was created by the authors.



(a) Deprivation



(b) Comorbidities



(c) Age

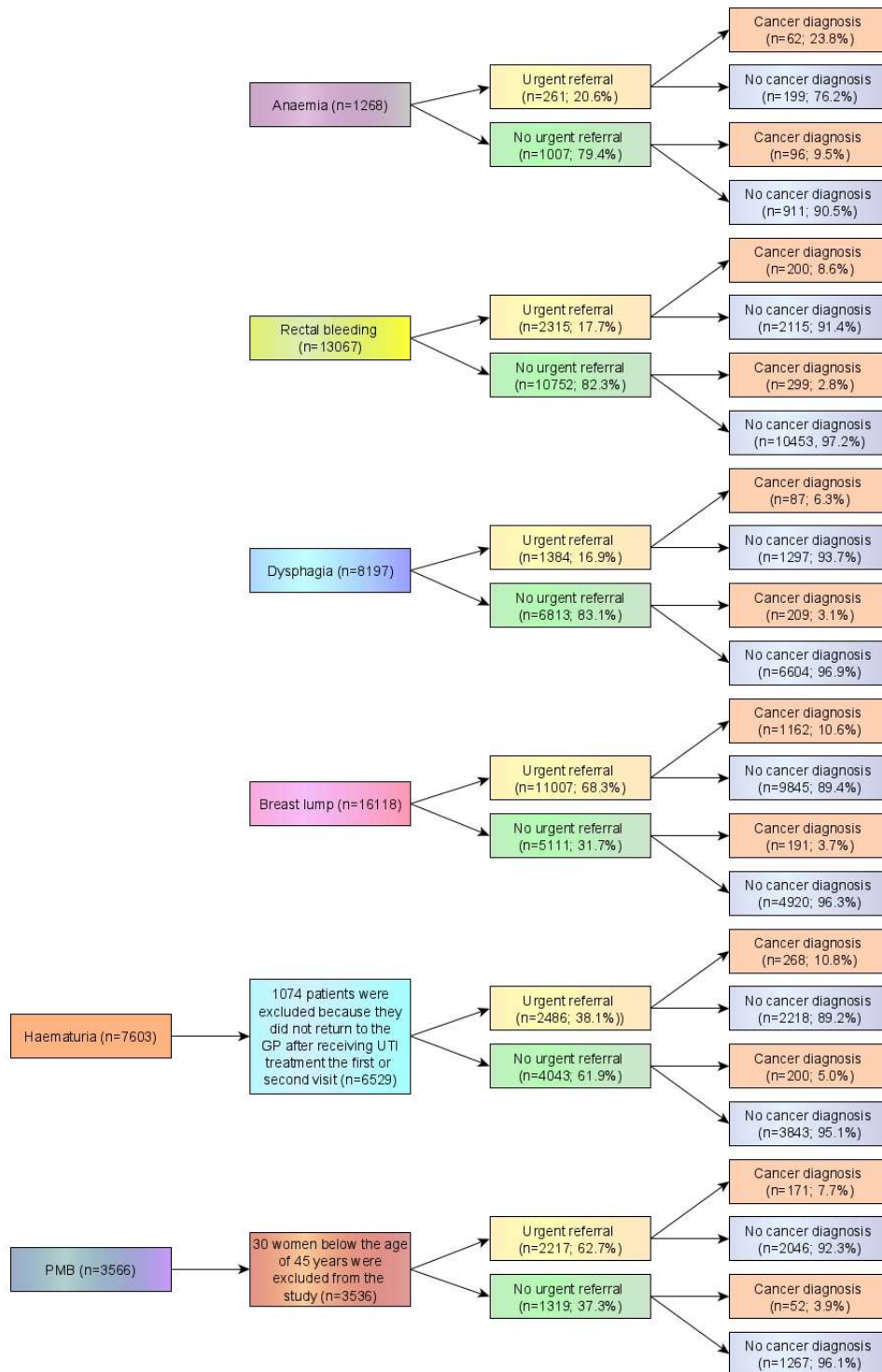


Figure A4. Flowchart of urgent suspected cancer referrals and cancer incidence per feature. This figure was created by the authors.

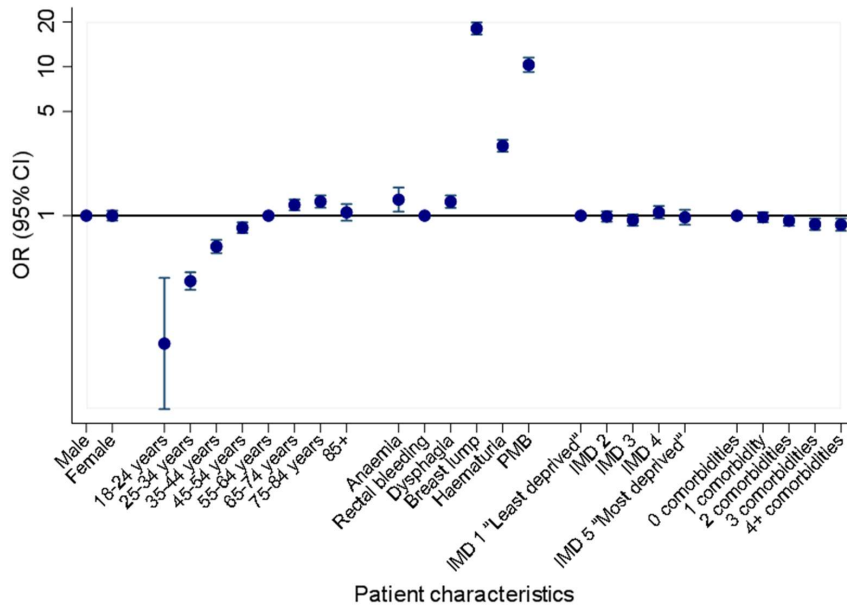


Figure A5. Associations between patient characteristics and receiving a two week wait referral within two weeks of visiting the GP. This figure was created by the authors.

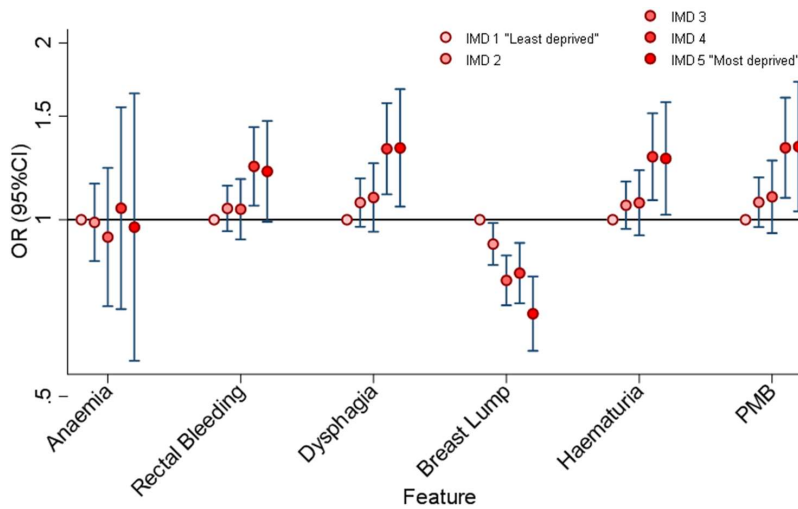


Figure A6. Interactions between deprivation level and feature type and their association with receiving a two week wait referral within two weeks of visiting the GP. This figure was created by the authors.

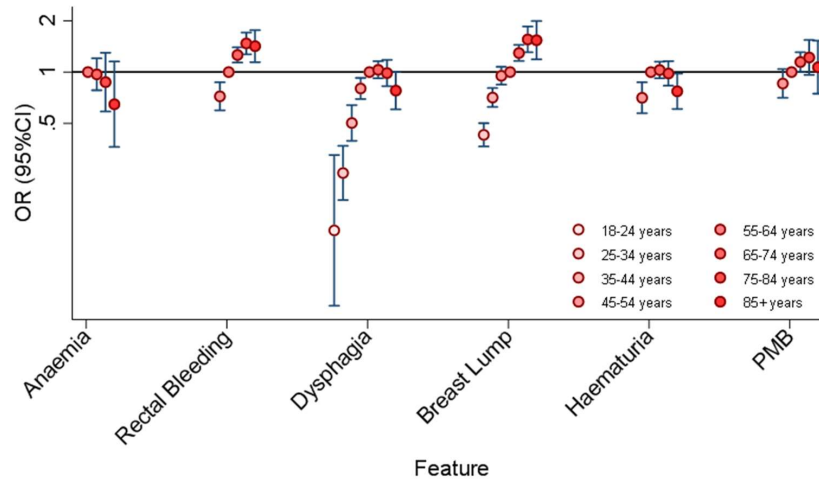


Figure A7. Interactions between age and feature type and their association with receiving a two week wait referral within two weeks of visiting the GP. This figure was created by the authors.