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Increased mortality in acromegaly is due to vascular and respiratory disease and is normalised by control of GH levels—A retrospective analysis from the UK Acromegaly Register 1970–2016

Steve Orme¹  | Richard McNally²  | Peter W. James²  | Jessica Davis³ | John Ayuk⁴ | Claire Higham⁵  | John Wass⁶ | the UK Acromegaly Register Study Group

¹Department of Endocrinology, St James's University Hospital Leeds, Leeds, UK

²Population Health Science Institute, Newcastle University, Royal Victoria Infirmary, Newcastle Upon Tyne, UK

³Society for Endocrinology, Bristol, UK

⁴Department of Endocrinology, Queen Elizabeth Hospital, Edgbaston, Birmingham, UK

⁵Department of Endocrinology, Christie Hospital NHS Foundation Trust, Division of Cancer Sciences, University of Manchester, Manchester, UK

⁶Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

Correspondence

Steve Orme, St James's University Hospital Leeds, 2 Leighton St, Leeds LS1 3EB, UK.
Email: orme.stephen@gmail.com

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Abstract

Context: Epidemiological studies involving patients with acromegaly have yielded conflicting results regarding cancer incidence and causes of mortality in relation to control of growth hormone (GH) excess.

Objective: The objective of this retrospective cohort study is to clarify these questions and identify goals for treatment and monitoring patients.

Methods: We studied 1845 subjects from the UK Acromegaly Register (1970–2016), obtaining cancer standardised incidence rates (SIR) and all causes standardised mortality rates (SMR) from UK Office for National Statistics, to determine the relationship between causes of mortality—age at diagnosis, duration of disease, post-treatment and mean GH levels.

Results: We found an increased incidence of all cancers (SIR, 1.38; 95% CI: 1.06–1.33, $p < .001$), but no increase in incidence of female breast, thyroid, colon cancer or any measure of cancer mortality. All-cause mortality rates were increased (SMR, 1.35; 95% CI: 1.24–1.46, $p < .001$), as were those due to vascular and respiratory diseases. All-cause, all cancer and cardiovascular deaths were highest in the first 5 years following diagnosis. We found a positive association between post-treatment and mean treatment GH levels and all-cause mortality ($p < .001$ and $p < .001$), which normalised with posttreatment GH levels of $<1.0 \mu\text{g/L}$ or meantreatment GH levels of $<2.5 \mu\text{g/L}$.

Conclusion: Acromegaly is associated with increased incidence of all cancers but not thyroid or colon cancer and no increase in cancer mortality. Excess mortality is due to vascular and respiratory disease. The risk is highest in the first 5 years following diagnosis and is mitigated by normalising GH levels.

KEYWORDS

cancer incidence rates, control of GH levels, mortality rates, UK Acromegaly Register

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1 | INTRODUCTION

Acromegaly is a rare chronic disease caused by excess growth hormone (GH) secretion, usually from a pituitary adenoma. It is associated with characteristic phenotypic features and metabolic perturbations which may lead to hypertension, arthropathy and diabetes mellitus.¹

Diabetes mellitus occurs in a significant proportion of patients with acromegaly and is associated with increased mortality, cardiovascular mortality, and morbidity.² However, GH and insulin-like growth factor 1 (IGF-1) levels do not appear to be predictive factors for the development of diabetes. On the contrary, age, body mass index and hypertension have been found to be significant risk factors, as in the general population.³

Wright et al.⁴ were the first to report an excess mortality due to cardiovascular disease in men, cerebrovascular disease in women and respiratory disease in both sexes. They reported no increase in mortality due to malignant cancer.

We previously studied a large cohort of patients with acromegaly in the United Kingdom and demonstrated no increase in cancer incidence or mortality, with increased mortality rates being positively correlated with post-treatment GH levels (fasting, mean of day curve or random) and when suppressed to $<2.5 \mu\text{g/L}$, this resulted in an overall mortality rate similar to the UK general population.⁵

Subsequent studies have reported cancer incidence rates slightly, but not significantly, below the German general population,⁶ no increase in cancer incidence in The French Acromegaly Register⁷ and no significant increase in cancer incidence rates in a Danish population, but increased cancer incidence due to breast, colon and other cancers in a meta-analysis of 23 studies (1957–2018).⁸ While the most deaths reported by the French Acromegaly Registry in 2017⁷ were due to cancer, there was no evidence of increased all-cause or cancer mortality rates. Published series have shown a reduction in mortality rates over the past 30 years.^{9,10} With the pattern of excess mortality variably reported as being due to malignant cancers⁹ and vascular disease.¹⁰

Established guidelines¹¹ recommend suppressing a post-treatment, random GH level $<1 \mu\text{g/L}$ and normalising age-specific IGF-1 levels. These are more stringent levels of biochemical control than those supported by a number of studies and there is some evidence that IGF-1 levels may not be the best predictor of outcome in acromegaly.¹² Moreover, post-treatment GH levels may not be the most reliable method of determining cumulative GH exposure in subjects with acromegaly.¹³

We studied a cohort of 1845 subjects from the UK Acromegaly Database and obtained cancer standardised incidence rates (SIRs) and all causes standardised mortality rates (SMRs) for the study and general population from the UK Office for National Statistics (ONS), to determine the relationship between causes of mortality and age at diagnosis, time since diagnosis, post-treatment, and mean treatment (day averaged) GH levels.

2 | METHODS

2.1 | Study design and participants

The UK Acromegaly Register was established in 1997 as a multi-centre collaborative project and adopted by the Society for Endocrinology in 2002. This project was approved by UK Multicentre Research Ethical Research Committee (MREC 03/5/76), given NHS R&D approval and adopted by UK Comprehensive Research Network (Project 03/5/0761 RAS 33824).

All subjects gave written informed consent for linkage of identifiable data with other UK data sources, such as Office for National Statistics (ONS), for death certification data, and cancer registries. Demographic data, clinical data (including serial GH levels) and different modalities of treatment were entered into the database by staff from each centre (see details from previous publications).^{14–16}

For this study, as we were attempting to define goals for treatment rather than determine the efficacy of specific treatment modalities, we did not analyse the effects of pituitary surgery, radiotherapy or medical treatments.

During the period under study (1970–2016), several international standards for GH were routinely used in teaching centres throughout the United Kingdom. The assays progressed from polyclonal radioimmunoassays to monoclonal 2-site immunoassays, and the standard reporting of GH results in the United Kingdom switched from mU/L to $\mu\text{g/L}$ in 2008. Before 2008 we used the conversion factor 2.5 to convert GH levels from mU/L to $\mu\text{g/L}$. GH levels were recorded throughout the lifetime of each patient. We used the last recorded GH level in the database (post-treatment GH level) and mean treatment (day averaged) GH levels (all GH levels measured throughout the lifetime of each subject, the frequency of which varied from centre to centre, averaged over the time the subject was in the study), in our analysis.

We studied a cohort of 1845 subjects, in which we were able to obtain death certification and cancer registry data (31,768 patient years), from 1970 or the date of diagnosis until the end of 2016, the date of death or removal from the database (75% of subjects were diagnosed from 1987 onwards). Demographic data was used to trace subjects to determine causes of death or cancer incidence, through the UK Office of National Statistics and cancer registries.

Causes of death and cancer registrations were coded using the International Classification of Diseases (ICD) 9 for cancer registrations and deaths occurring before 1999 and ICD 10 thereafter. For each cohort member person-years at risk were calculated by age, sex, and calendar year—commencing on the date of diagnosis of acromegaly and finishing on the date of diagnosis of cancer or death, exit from the ONS Registry, 85th birthday or end of December 2016, when the data set was frozen.

2.2 | Statistical analysis

Cause-specific death rates and cancer incidence rates were obtained by age, sex, and time-period from 0 to 85 years of age for the period of the study. Expected deaths or cancer incidences by cause were calculated by multiplying age-, sex-, and period-specific person-years at risk within the cohort by corresponding national cause-specific mortality rates or site-specific cancer rates using Stata and Excel.

SIRs and SMRs were calculated, and significant excess mortality or cancer incidence was determined by calculating a one-sided Poisson probability. Ninety-five percent confidence intervals (CIs) for SIRs and SMRs were calculated using the "exact method" by Sahai and Khurshid.¹⁷

We investigated linear trends in risk, post-treatment and mean treatment (day averaged) GH levels; age at diagnosis and time since diagnosis, using a χ^2 test for linear trends. We compared post-treatment GH levels <1 versus 1–2.5 $\mu\text{g/L}$ using a χ^2 test. A one-sided Poisson probability was calculated as we were testing several prior hypotheses relating to increased cancer incidence and all causes mortality in acromegaly (see Section 1). Statistical significance was defined as a $p < .05$.

3 | RESULTS

We studied a cohort of 1845 subjects with acromegaly (31,768 person years) and found an increased incidence of all cancers (SIR, 1.19; 95% CI: 1.06–1.33, $p < .001$), but not female breast (SIR, 0.95; 95% CI: 0.67–1.31, $p = .640$), thyroid (SIR, 2.89; 95% CI: 0.79–7.40, $p = .052$) or colon cancer (SIR, 1.23 95% CI: 0.80–1.80, $p = .169$). There was, however, some evidence of increased prostate cancer incidence (SIR, 1.36; 95% CI: 0.95–1.87, $p = .044$) (see Table 1).

There were no deaths attributable to thyroid cancer and there was no increase in mortality rates, due to all cancers, female breast, colon or prostate cancer (see Table 2).

We found an increase in all-cause mortality (SMR, 1.35; 95% CI: 1.24–1.46, $p < .001$), with the major contributors to this being cardiovascular disease (SMR, 1.38; 95% CI: 1.16–1.63, $p < .001$), cerebrovascular disease (SMR, 1.49; 95% CI: 1.10–1.97, $p = .006$) and respiratory disease (SMR, 1.55; 95% CI: 1.22–1.93, $p < .001$) (see Table 2).

There was no relationship between age at diagnosis and all cancer mortality, or mortality due to vascular or respiratory disease. Similarly, there was no relationship between age at diagnosis and all-cause mortality (0–24 years SMR, 1.88; 95% CI: 1.41–2.4, 25–59 years SMR, 1.31; 95% CI: 1.17–1.47 and 60+ years SMR 1.30; 95% CI: 1.13–1.50 χ^2 test for linear trend $p = .189$) (data not shown).

Table 3 demonstrates the negative association between time since diagnosis of acromegaly and all-cause mortality ($p < .001$), cardiovascular disease ($p = .050$) and all cancer mortality ($p = .007$). There was no relationship between time since diagnosis of acromegaly and mortality due to respiratory or cerebrovascular disease. The highest mortality rates were found in the first 5 years

TABLE 1 Summary of cancer incidence data.

Cancer site	Actual	Expected	SIR	95% CI	p Value
Breast	38	39.91	0.95	0.67–1.31	.640
Lung	40	38.58	1.04	0.74–1.41	.431
Colon	26	21.11	1.23	0.80–1.80	.169
Rectum	7	10.25	0.68	0.27–1.41	.885
Thyroid	4	1.38	2.89	0.79–7.40	.052
Prostate	37	27.30	1.36	0.95–1.87	.044
All cancers	321	269.86	1.19	1.06–1.33	.001

Abbreviations: CI, confidence interval; SIR, standardised incidence rates.

TABLE 2 Summary of mortality data.

Cause of death	Actual	Expected	SMR	95% CI	p Value
Female breast cancer	7	11.38	0.62	0.25–1.27	.936
Lung cancer	28	32.10	0.87	0.58–1.26	.789
Colon cancer	11	8.75	1.26	0.63–2.25	.265
Rectal cancer	1	3.91	0.26	0.01–1.42	.980
Prostate cancer	5	5.00	1.00	0.11–1.88	.385
All cancers	127	135.78	0.94	0.78–1.11	.786
Cardiovascular disease	136	98.46	1.38	1.16–1.63	<.001
Cerebrovascular disease	48	32.27	1.49	1.10–1.97	.006
Respiratory disease	78	50.38	1.55	1.22–1.93	<.001
All-cause	556	412.74	1.35	1.24–1.46	<.001

Abbreviations: CI, confidence interval; SIR, standardised incidence rates.

following diagnosis: all-cause mortality (SMR, 6.02; 95% CI: 4.59–7.75), cardiovascular disease (SMR, 6.02; 95% CI: 3.2–10.29) and all cancers (SMR, 7.25; 95% CI: 4.49–7.75).

Mortality rates due to cardiovascular disease ($p = .032$), cerebrovascular disease ($p = .001$), respiratory disease ($p < .001$) all cancers ($p < .001$) and all-cause mortality ($p < .001$) were positively correlated with post-treatment GH levels, with all-cause SMRs trending towards those of the reference population with post-treatment GH levels of <2.5 $\mu\text{g/L}$ (SMR, 1.15; 95% CI: 1.03–1.28, $p < .001$) [Table 4].

Table 5 shows a positive correlation between mean (day averaged) GH levels and all-cause mortality ($p < .001$), mortality to all cancers ($p < .001$) and mortality due to cardiovascular ($p = .001$), cerebrovascular ($p = .004$) and respiratory diseases ($p < .001$). The SMRs due to all causes fell to within the population normal range, with mean GH levels of <2.5 $\mu\text{g/L}$ (SMR, 1.0; 95% CI: 0.86–1.16, $p < .001$).

There appears to be a further reduction in all-cause mortality ($p < .001$), cardiovascular disease ($p = .009$) and all cancers ($p < .001$),

TABLE 3 Relationship between time since diagnosis of acromegaly and mortality.

Cause of death	SMR (95% CI), duration of acromegaly			χ^2 test for linear trend (p)
	<5 years	5–10 years	10+ years	
Cardiovascular disease	6.02 (3.20–10.29)	2.77 (1.69–4.27)	1.16 (0.94–1.40)	.050
Cerebrovascular disease	5.04 (1.37–12.91)	4.01 (1.93–7.38)	1.17 (0.81–1.64)	.187
Respiratory disease	4.88 (1.96–10.06)	2.47 (1.19–4.55)	1.36 (1.04–1.74)	.246
All cancers	7.25 (4.49–11.08)	1.30 (0.69–2.22)	0.76 (0.61–0.93)	.007
All-cause	6.02 (4.59–7.75)	2.42 (1.90–3.03)	1.13 (1.03–1.25)	<.001

Abbreviations: CI, confidence interval; SMR, standardised mortality rates.

TABLE 4 Relationship between post-treatment GH level and mortality.

Cause of death	SMR (95% CI), post-treatment GH Level			χ^2 test for linear trend (p)
	<2.5 $\mu\text{g/L}$	2.5–9.9 $\mu\text{g/L}$	$\geq 10.0 \mu\text{g/L}$	
Cardiovascular disease	1.33 (1.07–1.63)	1.40 (0.96–1.97)	1.85 (0.98–3.16)	.032
Cerebrovascular disease	1.26 (0.83–1.83)	1.90 (1.09–3.09)	2.12 (0.69–4.94)	.001
Respiratory disease	1.35 (1.00–1.80)	1.80 (1.11–2.75)	2.49 (1.07–4.90)	<.001
All cancers	0.73 (0.57–0.91)	1.67 (1.22–2.23)	1.15 (0.5–2.27)	<.001
All-cause	1.15 (1.03–1.28)	1.73 (1.47–2.02)	2.27 (1.72–2.95)	<.001

Abbreviations: CI, confidence interval; GH, growth hormone; SMR, standardised mortality rates.

TABLE 5 Relationship between mean treatment (day averaged) GH level and mortality.

Cause of death	SMR (95% CI), Mean GH Level			χ^2 test for linear trend (p)
	<2.5 $\mu\text{g/L}$	2.5–9.9 $\mu\text{g/L}$	$\geq 10.0 \mu\text{g/L}$	
Cardiovascular disease	1.23 (0.91–1.63)	1.35 (1.02–1.74)	2.07 (1.33–3.08)	.001
Cerebrovascular disease	1.19 (0.67–1.96)	1.64 (1.05–2.44)	2.33 (1.07–4.43)	.004
Respiratory disease	0.85 (0.50–1.34)	2.01 (1.46–2.70)	1.94 (0.93–3.57)	<.001
All cancers	0.66 (0.47–0.90)	1.22 (0.95–1.54)	1.16 (0.65–1.92)	<.001
All-cause	1.00 (0.86–1.16)	1.50 (1.33–1.69)	2.28 (1.85–2.79)	<.001

Abbreviations: CI, confidence interval; GH, growth hormone; SMR, standardised mortality rates.

but not cerebrovascular disease or respiratory disease on suppressing post-treatment GH levels to $<1 \mu\text{g/L}$ compared with a post-treatment GH level of 1–2.5 $\mu\text{g/L}$. With all-cause mortality being consistent with the UK reference population (SMR, 1.03; 95% CI: 0.89–1.18, $p < .001$), when this goal is achieved (see Table 6).

4 | DISCUSSION

This is the largest epidemiological study of cancer incidence and all-cause mortality in acromegaly, associating SMR with post-treatment and mean GH levels, published to date. Using the UK Acromegaly Register we identified a cohort of subjects and cancer registration

data and death certification data from subjects and the UK reference population to calculate SIRs and SMRs, thus limiting the effect of ascertainment bias for cancer incidence data and eliminating bias for mortality data.

In this study, we were not able to use measures of IGF-1, due to a paucity of data and the fact that they were measured on several different assays in centres throughout the United Kingdom, which changed during the study period (1970–2016) and were therefore not readily comparable. Because IGFBP3 levels are not regularly measured in clinical practice in the United Kingdom, and both IGF-1 and IGFBP3 levels are elevated in acromegaly, the former associated with cancer development and the latter with a reduction in cancer risk¹⁸ and GH rather than IGF-1 levels have been found to predict

TABLE 6 Comparison between mortality with post-treatment GH levels <1 and 1–2.5 µg/L.

Cause of death	SMR (95% CI), post-treatment GH Level		χ^2 test (p)
	<1 µg/L	1–2.5 µg/L	
Cardiovascular disease	1.30 (0.98–1.69)	1.38 (0.96–1.92)	.009
Cerebrovascular disease	1.17 (0.66–1.93)	1.38 (0.71–2.41)	.287
Respiratory disease	1.26 (0.84–1.82)	1.51 (0.92–2.34)	.039
All cancers	0.52 (0.36–0.72)	1.14 (0.81–1.55)	<.001
All-cause	1.03 (0.89–1.18)	1.38 (1.16–1.62)	<.001

Abbreviations: CI, confidence interval; GH, growth hormone; SMR, standardised mortality rates.

excess mortality in acromegaly,^{12,13} we relied upon GH levels rather than GH and IGF-1 levels in this study.

We found an increased incidence of all cancers, but not female breast, thyroid, or colon cancer. There was, however, some evidence of an increased incidence of prostate cancer. Prostate cancer incidence has risen, with a decline in mortality in developed countries over the period of this study. This temporal change has been attributed to lifestyle patterns (obesity, fitness, higher incidence of diabetes mellitus and dietary factors)¹⁹ but also the increasing measurement of prostate-specific antigen (PSA). In a cohort of closely monitored patients with acromegaly who are likely to be on testosterone replacement, higher frequency of PSA measurement may have resulted in higher levels of detection of occult prostate cancer, while there was no evidence of an increased prostate cancer mortality in this cohort (see Table 2).

An increased incidence of breast cancer in women with acromegaly was originally reported by Nabarro.²⁰ He reported no cases of colon cancer. Other series have reported an excess cancer incidence, including colon cancer incidence in men with acromegaly discharged from VA hospitals (colonic neoplasms SIR, 3.1; 95% CI: 1.7–5.1).²¹ This has led to a large number of studies to determine the incidence of colonic polyps and colon cancers in patients with acromegaly, although genetic and environmental factors have been reported to be of greater importance.²² More recent studies have shown cancer incidence rates slightly, but not significantly below the German population,⁶ with no increased cancer incidence in a French acromegaly cohort⁷ and slightly, but not significantly increased incidence in a Danish acromegaly cohort.⁸ The authors also performed a meta-analysis of 23 studies (1957–2018) and showed increased cancer incidence rates in colon, breast, and other malignancies.⁸ However, two of the largest studies reported included Mustacchi and Shimkin,²³ which reflects a cohort of patients with acromegaly very different from the present day, and even pre-dates the GH radio-immunoassay, and Ron et al.,²¹ previously mentioned, only studied men and compared cancer incidence in subjects with acromegaly and other patients discharged from VA hospitals. Using different methods of ascertainment and demographically disparate populations means that these studies are not directly comparable. The largest study, in terms of person years follow up, and the

reference population, Orme et al. showed no excess cancer incidence.⁵

In contrast to the cancer incidence data, we found no increase in mortality due to all cancer or prostate cancer. There was no increase in mortality due to female breast or colon cancer, and no deaths attributed to thyroid cancer. As data for both subjects and the UK reference population are drawn from death certification, there can be no ascertainment bias. The data is consistent with the previously quoted Danish study, which reported on overall increase in mortality (SMR 1.3), with no increase in cancerspecific mortality.⁸

There was an increase in all-cause mortality (SMR 1.35), which was lower than shown by Orme et al.⁵ (SMR 1.6) and is consistent with the reduction in mortality reported from The Swedish National Health Registries between 1987 and 2013¹⁰ and a meta-analysis of mortality in acromegaly studies, published before and following 2008, in which the mean SMR fell from 1.76 to 1.26.^{9,24} These data reflect an improvement in overall mortality in acromegaly in the UK population from 1995 to 2016 (the dates when the respective datasets were closed). The major contributors to the excess mortality were vascular and respiratory diseases.

Mortality in acromegaly due to all-causes, cardiovascular disease and all cancers are negatively related to time since diagnosis. With the highest SMRs occurring in the first 5 years following diagnosis. As mortality due to these conditions was related to post-treatment and day-weighted averaged GH levels, the fall in mortality rates appear to be due to improved biochemical control of patients occurring early in their clinical course.

We found a positive relationship between all-cause, cardiovascular, cerebrovascular, and respiratory mortality and post-treatment GH levels. Moreover, despite there being no overall increase in mortality from any form of cancer, mortality due to all cancers was positively correlated with post-treatment GH levels and fell well within the UK population reference range with levels of <2.5 µg/L. This study builds on the finding of our previous research, Orme et al. which showed an increase all-cause and cardiovascular mortality, but no increase in mortality due to malignant disease. There was a positive correlation between mortality due to malignant disease and post-treatment GH levels. All-cause mortality and cardiovascular mortality were also positively correlated with post-treatment GH

levels, with normalisation of all-cause mortality rates with post-treatment GH levels $<2.5 \mu\text{g/L}$.⁵

In summary, we have studied a cohort of patients from the UK Acromegaly Register to show an increase in cancer incidence but no increase in thyroid or colon cancer incidence and there was no increase in cancer mortality. These data and a recent systematic review²⁵ call into question the practice of thyroid and colon cancer screening in patients with acromegaly, above that of the general population.

Mortality rates are highest in the first 5 years after diagnosis and can be normalised by lowering mean treatment (day averaged) GH levels to $<2.5 \mu\text{g/L}$ or post-treatment GH levels to $<1 \mu\text{g/L}$, in line with current international treatment guidelines.¹¹ This data supports the practice to normalise GH hypersecretion as swiftly as possible to reduce excess mortality.

AUTHOR CONTRIBUTIONS

Richard McNally and Peter W. James performed the statistical analysis and data interpretation. Jessica Davis collected data and collated death certification and cancer incidence data. Steve Orme designed the study, wrote the manuscript, and contributed to data interpretation. John Ayuk, Claire Higham, and John Wass contributed to discussions regarding the study. All authors critically reviewed and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets generated and/or analysed during the current study are not publicly available but can be obtained from the corresponding author on reasonable request.

ORCID

Steve Orme  <http://orcid.org/0009-0002-3174-5585>

Richard McNally  <http://orcid.org/0000-0001-6685-6467>

Peter W. James  <http://orcid.org/0009-0005-2407-5984>

Claire Higham  <http://orcid.org/0000-0002-0917-9743>

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APPENDIX

See Table A1

TABLE A1 Principal investigators—UK Acromegaly Register Study Group.

Aberdeen	Dr. Prakash Abraham
Belfast	Dr. Steven Hunter
Birmingham	Dr. John Ayuk
Bradford	Dr. Steve Peacey
Brighton	Dr. Anna Crown
Bristol	Dr. Karin Bradley
Cambridge	Prof. Mark Gurnell
Cardiff	Prof. Aled Rees
Chester	Dr. Frank Joseph
Dundee	Prof. Graham Leese
Edinburgh	Dr. Fraser Gibb
Exeter	Dr. Bijay Vaidya
Glasgow	Dr. Colin Perry
Hull	Prof. Thozhukat Sathyapalen
Leeds	Dr. Steve Orme (retired)
Leicester	Dr. Narendra Reddy
Liverpool (RULH)	Dr. T Purewal
London (Barts)	Prof. Maralyn Druce
London (Kings)	Dr. Simon Aylwin
London (UCLH)	Prof. Stephanie Baldeweg
Manchester (The Christie)	Prof. Peter Trainer (retired) Dr. Claire Higham
Manchester (Hope)	Dr. Tara Kearney
Manchester (MRI)	Dr. Steve Ball
Newcastle	Dr. Yaasir Mamoojee
Norfolk and Norwich	Dr. Francesca Swords
Oxford	Prof. Jeremy Tomlinson
Oxford	Dr. Aparna Pal
Plymouth	Dr. Daniel Flanagan
Preston	Dr. Simon J. Howell
Sheffield	Prof. John Newell-Price
Stoke	Dr. Biju Jose
Watford	Dr. Colin Johnston
York	Dr. Paul Jennings (retired)