BMC Pulmonary Medicine

Research article

Primary ciliary dyskinesia (Siewert's / Kartagener's Syndrome): Respiratory symptoms and psycho-social impact

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Published: 27 November 2003

BMC Pulmonary Medicine 2003, **3**:4

Received: 29 July 2003
Accepted: 27 November 2003

This article is available from: http://www.biomedcentral.com/1471-2466/3/4

Abstract

Background: Although the pathophysiological defect in primary ciliary dyskinesia (PCD; Siewert's / Kartagener's syndrome) is now well characterised, there are few studies of the impact of the condition upon health function, particularly in later life. This study assesses the health impact of the condition in a large group of patients. In addition, it assesses the similarity in age of diagnosis, symptoms and problems of those with *situs inversus* (PCD-SI) and those with *situs solitus* (PCD-SS).

Methods: Postal questionnaire sent to members of the UK Primary Ciliary Dyskinesia Family Support Group. The questionnaire contained the St. George's Respiratory Questionnaire (SGRQ) and the SF-36 questionnaire for assessing health status.

Results: 93 questionnaires were returned, representing a 66% response rate. Replies were received from similar numbers of PCD-SI and PCD-SS. Individuals with PCD-SI did not show a significant tendency to be diagnosed earlier, and neither did they show any difference in their symptoms, or the relationship of symptoms to age. Respiratory symptoms were fairly constant up until the age of about 25, after which there was a slow increase in symptoms, and a decline in health status, patients over the age of 40 being about one and a half standard deviations below the mean on the physical component score of the PCS. Patients diagnosed earlier in life, and hence who had received more treatment for their condition, had better scores on the SGRQ Impact and Activity scores.

Conclusions: PCD is a chronic condition which has a progressively greater impact on health in the second half of life, producing significant morbidity and restriction of life style. Early diagnosis, and hence earlier treatment, may improve symptoms and the impact of the condition.

Background

The condition now known as Primary Ciliary Dyskinesia (PCD), a case of which was reported by Siewert [1], was first properly recognised by Kartagener [2,3], who

described bronchiectasis, nasal polyposis, and chronic sinusitis in a group of patients who also showed *situs inversus totalis*, the complete left-right reversal of the viscera [4]. Subsequent work by Afzelius [5] demonstrated that patients with Kartagener's syndrome had a motility defect in the cilia of respiratory mucosa, in the lungs and sinuses, and that in addition in males there can also be a defect of sperm motility, which results in reduced fertility [6].

Electron microscopy of mucosal cilia and sperm tails shows that in PCD the normal 9+2 architecture is disrupted due to the absence of dynein arms [7]. Since dynein is one of the key intra-cellular 'molecular motors' [7,8], the absence of the dynein arms is responsible for the impaired motility of the cilia and sperm. The identification of the ultra-structural ciliary defect means that it is now more appropriate to describe the condition as primary ciliary dyskinesia, the condition resulting from a primary problem in ciliary motility. The recognition of ciliary dyskinesia or immotility in Kartagener's syndrome has resulted in improved diagnosis, and an increasing awareness that the condition is more frequent than had been realised, and that, despite being an inherited defect, it is sometimes only diagnosed quite late in life [9,10]. Although the condition is usually inherited as an autosomal recessive [11,12], and some specific gene defects have been recognised [13,14], it is clear that the syndrome shows substantial genetic heterogeneity [15]

Although Kartagener's syndrome classically showed *situs inversus*, a 'partial' syndrome was also recognised historically in which all of the symptoms were present, but the viscera were normally oriented (*situs solitus*). It is now clear that such cases are equally as frequent as the full syndrome, that cases of the syndrome with or without *situs inversus* co-occur within families with an autosomal recessive pattern of inheritance, and that the proper phenotype is not *situs inversus* but is more likely to be random *situs*, with a 50:50 chance of the viscera showing the normal or the reversed pattern [16]. Such a model can therefore explaining the occasional occurrence of monozygotic twins with PCD, one showing *situs inversus* and the other *situs solitus* [17]. Although the precise causal mechanism for the development of random *situs*, has not been fully elucidated in PCD, work on *situs inversus* in a range of species, including mice, frogs, chicks and zebra-fish [18], suggests that the problem arises during development due to a ciliary defect in the nodal region (or its homologues of Hensen's node in the chick, or the Spemann organiser in amphibia, which are all associated with the protein known as left-right dynein [19,20]), which results in disrupted or random fluid flow [21,22] – for a semi-popular account see McManus [23]. There are however some problems with the theory, and ciliary function may not entirely explain laterality development [24,25]. Although there is no direct evidence that patients with PCD also show defects in the cilia in the nodal region, the simultaneous occurrence of defects both in 9+2 cilia and 9+0 cilia in *Hfh4* null mice [26], and in mice with the human DNAH5 mutation which occurs in PCD [27], suggests that it is probably the case.

Despite the structural basis of PCD now being well-understood, there have been few studies of the effects of the condition on the overall health status of patients (although there are studies of respiratory function e.g. [28]). In particular there is no systematic description of the pattern of respiratory and other symptoms, of their variability and their development over the life-span, and neither is there any account of the impact of the condition on the life-style of the patients, or its effect upon their mental health. A search of PubMed found 771 articles using the search term ("Primary ciliary dyskinesia" or Kartagener*) and 693195 articles using the search term (Psycholog* or social), but a joint search of these categories found only a single article, in Spanish, which was only a case report [29].

The prevalence of PCD in the UK is difficult to estimate precisely. Although a figure of 1 in 15,000 has been quoted, which may itself be an underestimate, that would mean there are about 70 new cases born each year, and about 3,000 patients in total [4].

Here we describe a study of a group of 93 patients with PCD who are all members of a Patient Support Group based in southern England (although patients came from all over the UK), and in whom respiratory symptoms have been measured using the St. George's Respiratory Questionnaire, and health status has been assessed using the SF-36 questionnaire.

Methods

A postal questionnaire was sent in January 2003 to all individuals on the mailing list of the UK's Primary Ciliary Dyskinesia Family Support Group. A reminder was sent to non-respondents after four weeks.

The questionnaire consisted of 16 pages of A4, and covered a wide range of topics, not all of which are relevant to the present study, since a study was also being carried out of lateralisation [30]. Measures of personality were also collected, but will be reported elsewhere [31]. Separate versions of the questionnaire were provided for adults and children (under 16 years of age). The principle difference was in the consent forms (see below), and in addition there were minor changes of wording between the two forms, principally to do with work/school, and with occasional simplification of wording in child version. The

child version also did not contain questions about smoking.

Respiratory symptoms were assessed by the St. George's Respiratory Questionnaire (SGRQ) [32-35], which provides three separate scales, **Symptoms, Activity** and **Impact**. It has been validated in bronchiectasis [34]. The scores are scaled in the range 0 – 100, where a score of 100 indicates optimal functioning within the context of respiratory illness.

Health Status overall was assessed by version 2 of the SF-36 questionnaire, which is a widely used generic instrument for assessing mental and physical functioning [36], for which UK population norms are also available [37]. The questionnaire has eight sub-scales which can be divided into two broad groups, **Physical Functioning, Role Physical, Bodily Pain**and **General Health** which are primarily physical, and **Energy/vitality, Social functioning, Role Emotional** and **Mental Health** which are primarily mental. The eight sub-scales are each scored in the range 0 – 100, where a score of 100 indicates optimal functioning. Factor analysis was used in the population-based survey to calculate weights for deriving two summary scores, the **Physical Component Summary** (PCS) and **the Mental Component Summary** (MCS) [37]. Unlike the sub-scales, the PCS and MCS are scored so that in the reference population the mean is 50, and the standard deviation is 10, meaning that 95% of the population score in the range 30–70. Separate age and sex-related norms are also available http://www.hsru.ox.ac.uk/sf36v2.htm.

The study was approved by the joint UCL/UCLH Committees on the Ethics of Human Research. The mailing also included a letter from the secretary of the Support Group which endorsed the study. In order to protect patient confidentiality, the names of members of the Support Group were not known to the researchers, address labels being applied to envelopes by the Support Group. Respondents were given the opportunity to provide contact details for further research, and a majority did so. The questionnaire contained a consent form as an integral part of its construction, and this was signed either by the patient, or, where appropriate, by the patient and their parent or guardian.

Results

Response rate

The initial mailing was to 160 addresses. Responses were received from 93 individuals, and a further 15 envelopes were returned by the Post Office as undeliverable for one reason or another. The response rate is therefore 93/(160-15) = 66%.

Respondents

Ninety-three completed questionnaires were returned, although not all respondents had replies to all questions (in some cases because of being too young). Parents of children were encouraged to respond to the questionnaire, irrespective of how young the child was, and to complete only those questions which it was possible to answer for the child. The age distribution was somewhat skewed, the mean being 22.7 years (SD 16.8), with the median being 16.5 (quartiles 10.8 and 31.3), and the 10^{th} and 90^{th} percentiles being 5.4 and 53.7). 59 (63.4%) respondents were female and 34 were male. The female respondents were somewhat older (Man-Whitney U test, p = .039; mean age of females = 25.2; mean age of males = 18.42) . Of those under the age of 16, 55% (24/44) were female, but for those over the age of 16, 71% (35/49) were female. The origin of the difference is not clear.

Situs inversus

48 respondents said that their heart was on the right, and 44 that their heart was on the left (one respondent did not answer this question). There is therefore no evidence of a response bias in favour of those with their heart on the right (χ^2 = 0.17, 1 df=, NS). All of the respondents who said that their heart was on the right said that this had been confirmed by X-ray, and all but two said that to their knowledge all of their body organs were reversed. It therefore seems safe to infer that there are 48 cases of Primary Ciliary Dyskinesia with *situs inversus* (PCD-SI), 44 cases of Primary Ciliary Dyskinesia with *situs solitus* (PCD-SS), and one of PCD with situs unknown.

Family history

Twenty respondents reported that other members of their family had PCD. There was no association with situs inversus, 10 of the 20 having PCD-SI and 10 having PCD-SS.

Age at diagnosis

Figure 1 shows the age at diagnosis in relation to age at the time of the survey for the PCD-SI and PCD-SS patients. The age at diagnosis was slightly lower in the PCD-SI group (9.1, SD 12.1; median = 5.0, IQR = .62 – 12.0, N = 29) than in the PCD-SS group (mean = 13.8 yrs, SD 16.6; median = 7.0, IQR = 1.2 – 24.1, N = 30), although the difference was not significant using either a t-test (t_{57} = 1.244, p = .219) or a Mann-Whitney U-test (z = 1.02, p = .306). The standard deviation in both groups was however very large, indicating that most of the older patients had only been diagnosed relatively recently (on average the patients over the age of 30 (mean = 46.6, SD 11.9), were 32.1 years old at diagnosis, i.e. mostly diagnosed within the past fifteen years – see figure 1). Multiple regression of age at diagnosis, after taking age into account, did find an almost significant difference between the PCD-SI and

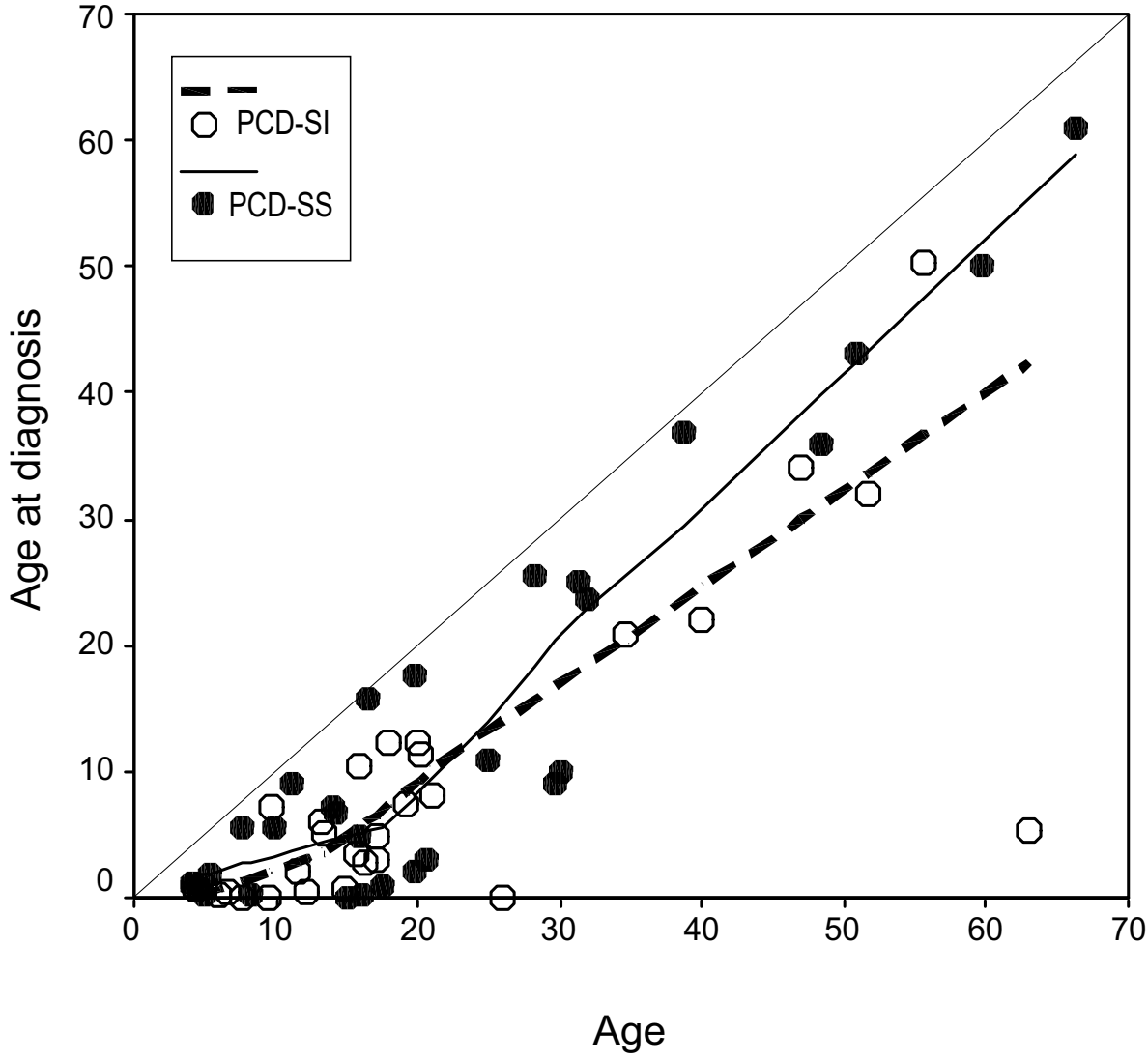

Figure 1
Age at diagnosis of PCD (ordinate), in relation to current age (abscissa), separately for patients with PCD-SI (open circles, dashed line), and PCD-SS (solid circles, solid line). The fitted lines are lowess curves.

PCD-SS groups (t_{56} = 1.919, p = .060), although the effect was principally due to the outlier, who was aged 63, but diagnosed at the age of five. Removal of that case resulted in a non-significant difference (t_{55} = 1.492, p = .141).

Smoking

A question on smoking was only included in the questionnaire sent to those over the age of sixteen. Two individuals (4%) were current smokers; both were male and smoked ten cigarettes per day. A further six (13%) were ex-smokers, and the remaining 37 (82%) had never smoked.

St. George's Respiratory Questionnaire

The three sub-scales of the St. George's Respiratory Questionnaire all correlated highly with one another (**Symptoms** with **Activity**, r = .663, p < .001; **Symptoms** with **Impact**, r = .779, p < .001; and **Activity** with **Impact**, r = .757, p < .001). The **Symptoms** sub-scale correlated significantly with age (r = -.479, p < .001), as also did the **Activity** sub-scale (r = -.387, p < .001), and the **Impact** sub-scale (r = -.401, p < .001). Figure 2 shows a lowess (locally weighted least-squares) plot of the relationship of the symptoms sub-scale to age. The **Symptom** score declines only very slightly until about the age of 25, after which the

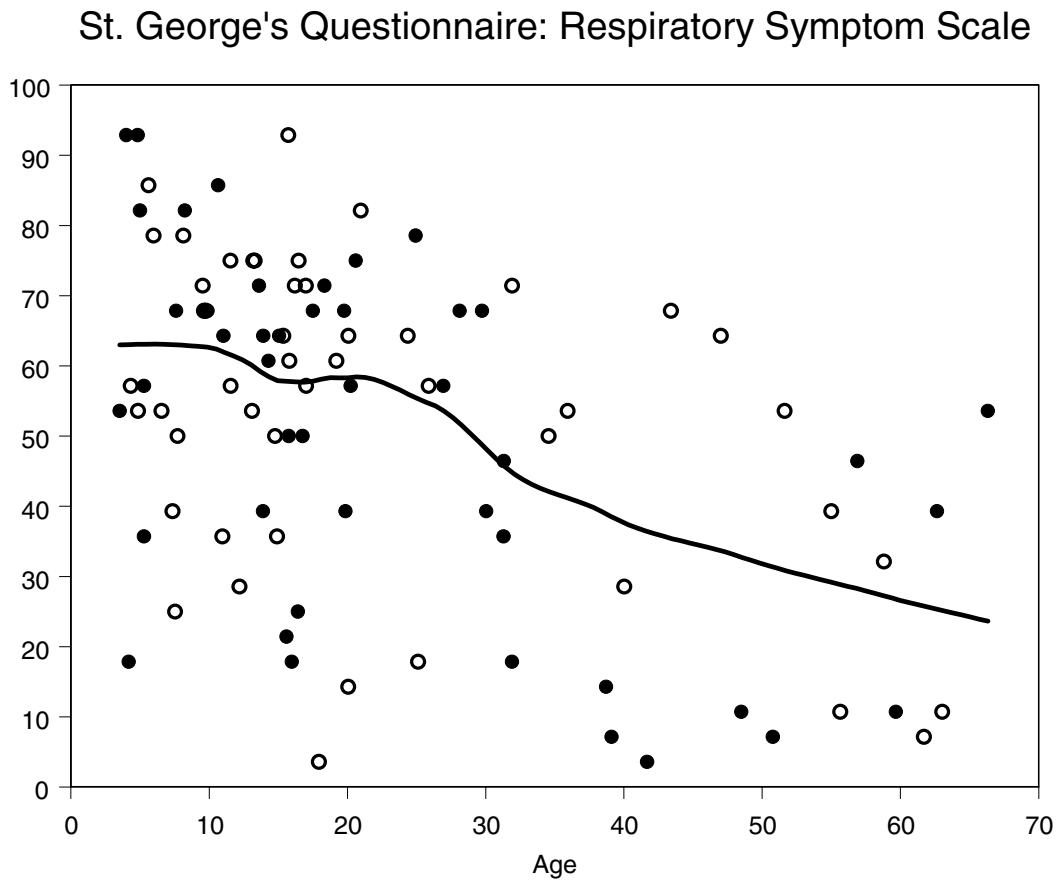

Figure 2
The Symptom scale of the St. George's Respiratory Questionnaire plotted in relation to the age of the respondent. PCD-SS individuals are shown as solid black circles (•) and PCD-SI individuals as open black circles (❍). The solid black line is the lowess curve fitted through the data.

score declines somewhat more rapidly and there is a worsening of respiratory symptoms. Although not shown, the **Activity** and **Impact** sub-scales show a similar relationship with age.

The SF-36 measures of Health Status

Although the eight sub-scales of the St. George's Respiratory Questionnaire provide a detailed picture of health status, the vast majority of the variance in them is more simply described by the physical component score and mental component scores. These scores also have the advantage of well-described population norms. Both the PCS and the MCS in our sample show a significant correlation with age ($r = -.344$, $p < .001$; $r = -.363$, $p < .001$ respectively). However the population norms also show a decline associated with normal ageing, and therefore on its own this correlation is difficult to interpret. Figures 3 and 4 show scattergrams and lowess curves of the PCS and MCS in relation to age, and in relation to population norms for the age ranges 16–24, 25–34, 35–44, 45–54 and 55–64. The lowess curve in figure 3 shows that the PCS is only about half a standard deviation below the population mean until the mid-20s, after which the score declines somewhat more rapidly than the population norms, and from about the age of 40 or so it is about one and a half standard deviations below the norms. In contrast, although figure 4 shows that the MCS also declines with age, the declining health status broadly parallels that found in the general population as a whole, being at most about one third to one half a standard deviation below the population norms.

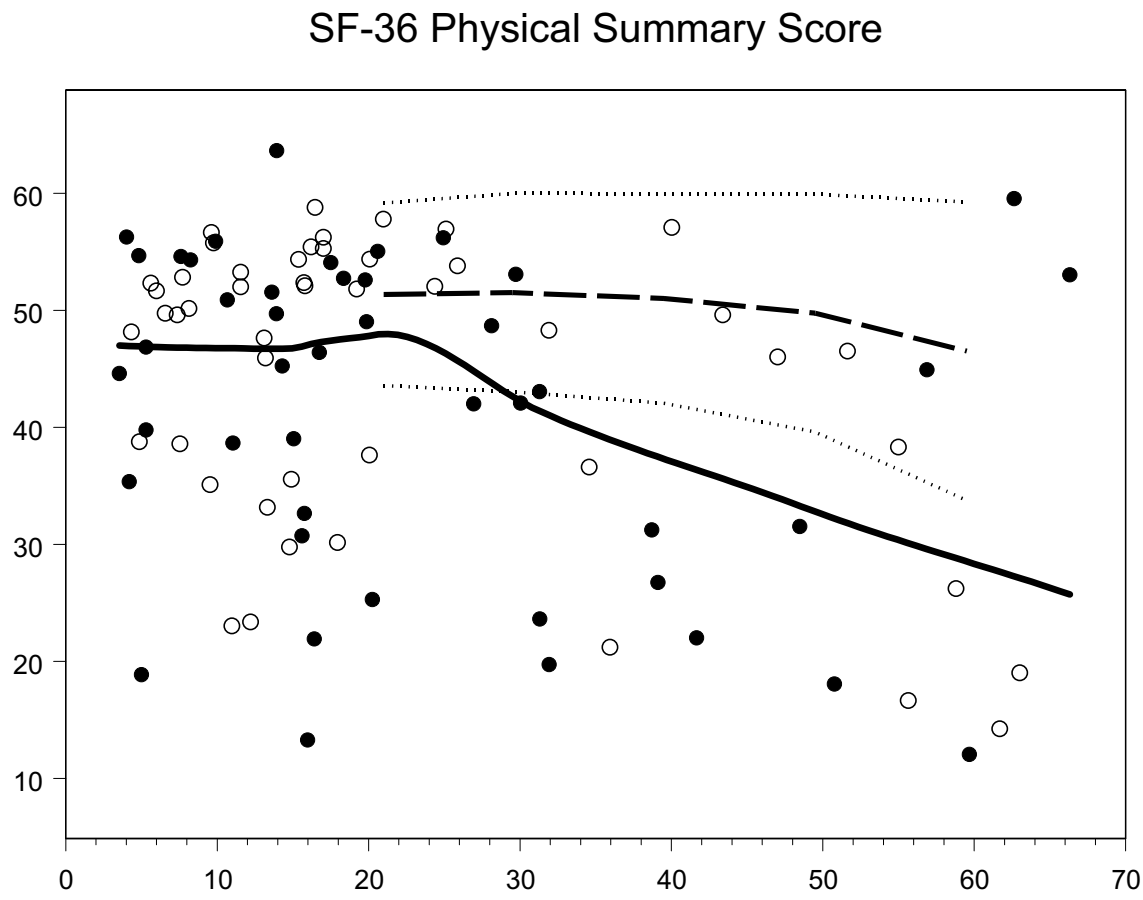

Figure 3
The Physical Component Score of the SF-36 Health Status measure, plotted in relation to the age of the respondent. PCD-SS individuals are shown as solid black circles (•) and PCD-SI individuals as open black circles (❍). The solid black line (**-**) is the lowess curve fitted through the data. The dashed black line (- - -) shows the population norm (see text), and the dotted black lines (.....) show one standard deviation above and below the population norm.

Age at diagnosis in relation to symptoms

An important question concerns the impact of the age at diagnosis upon symptoms. An earlier diagnosis allows the possibility of medically based interventions to try and prevent the longer-term complications of the condition. Statistically the best way to visualise this is in terms of 'time since diagnosis' (i.e. Current Age minus Age at Diagnosis) since that is the time during which medical care was provided. If medical care has an effect upon symptoms, then time since diagnosis should provide an additional predictor of symptom score, after age has been taken into account. Table 1 firstly shows the regression of symptom scores upon age, and then shows the regression of scores upon age and time since diagnosis (with each effect taking the other into account). The SF-36 physical and mental scores, and the SGRQ **Symptoms** score do not show a significant effect of time since diagnosis. However the SGRQ **Impact** score shows a statistically significant effect of time since diagnosis ($p = .022$), and the regression coefficient is positive (.580), in contrast to the negative regression coefficient for age (-.599) – in other words, despite a decline in score with each year of age, there has been an *increase* due to each year of treatment. Furthermore, since the regression coefficients are unstandardised, and hence are on the same scale of SGRQ points/year, then the effect of age, and the effect of time since diagnosis are equivalent, but with opposite signs, suggesting that the two effects balance one another out so that deterioration has

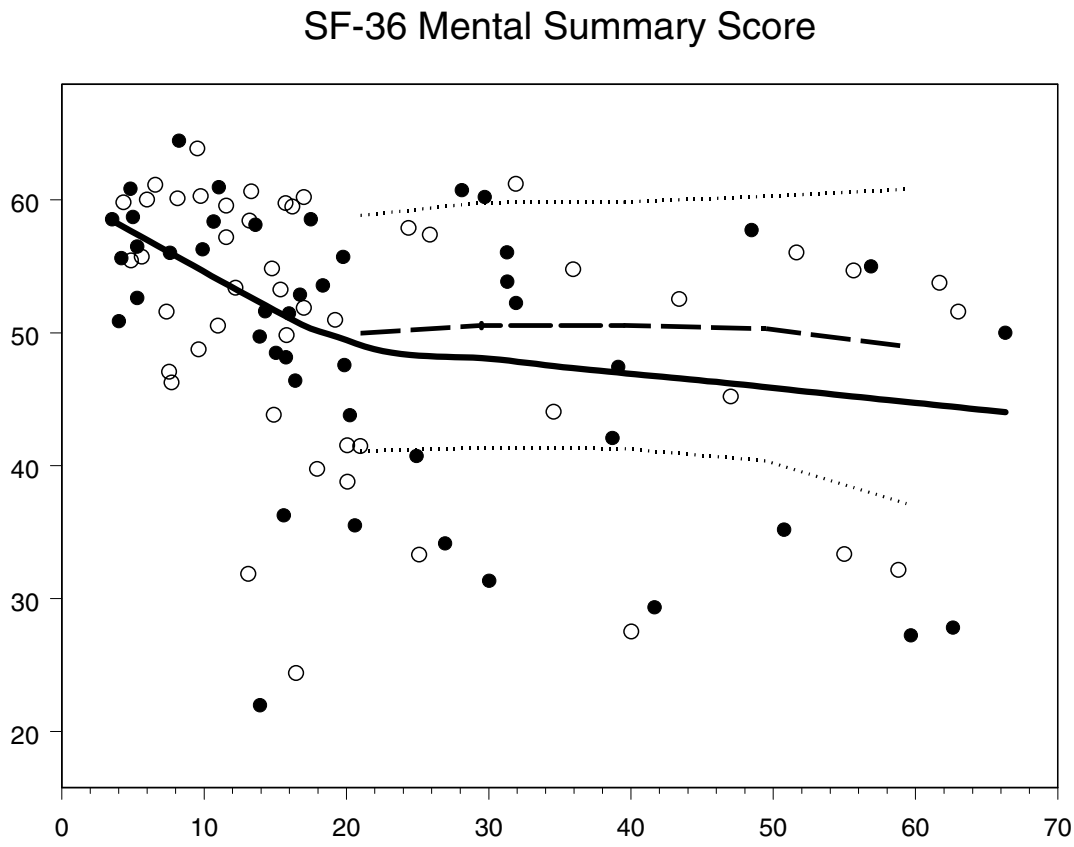

Figure 4
The Mental Component Score of the SF-36 Health Status measure, plotted in relation to the age of the respondent. PCD-SS individuals are shown as solid black circles (•) and PCD-SI individuals as open black circles (❍). The solid black line (**-**) is the lowess curve fitted through the data. The dashed black line (- - -) shows the population norm (see text), and the dotted black lines (.....) show one standard deviation above and below the population norm.

Table 1: Regression of the effects of age and time since diagnosis upon symptom scores. Column (1) shows the simple regression of symptom score upon age, without taking time since diagnosis into account.

	Effect of age, without taking time since diagnosis into account (1) b (SE) Sig	Effect of age, taking time since diagnosis into account (2) b (SE) Sig	Effect of time since diagnosis, taking age into account (3) b (SE) Sig
SGRQ-Symptoms	**-.750 (.171) p < .001**	**-.832 (.191) p < .001**	.354 (.363) p = .334
SGRQ-Activity	**-.500 (.172) p = .005**	**-.646 (.188) p = .001**	**.628 (.359) p = .085**
SGRQ-Impact	**-.465 (.121) p < .001**	**-.599 (.129) p < .001**	**.580 (.246) p = .022**
SF-36: PCS	**-.292 (.105) p = .007**	**-.328 (.117) p = .007**	.159 (.223) p = .480
SF-36: MCS	**-.216 (.073) p = .005**	**-.241 (.082) p = .005**	.106 (.156) p = .500

Column (2) shows the regression of symptom score upon age after taking time since diagnosis into account, and column (3) shows the regression of symptom score upon time since diagnosis after taking age into account. The effects in columns (2) and (3) are therefore statistically independent. Regression coefficients are shown as the 'b' (unstandardised) coefficients, along with their standard error (SE) and significance levels (p). Entries in bold have p < .1.

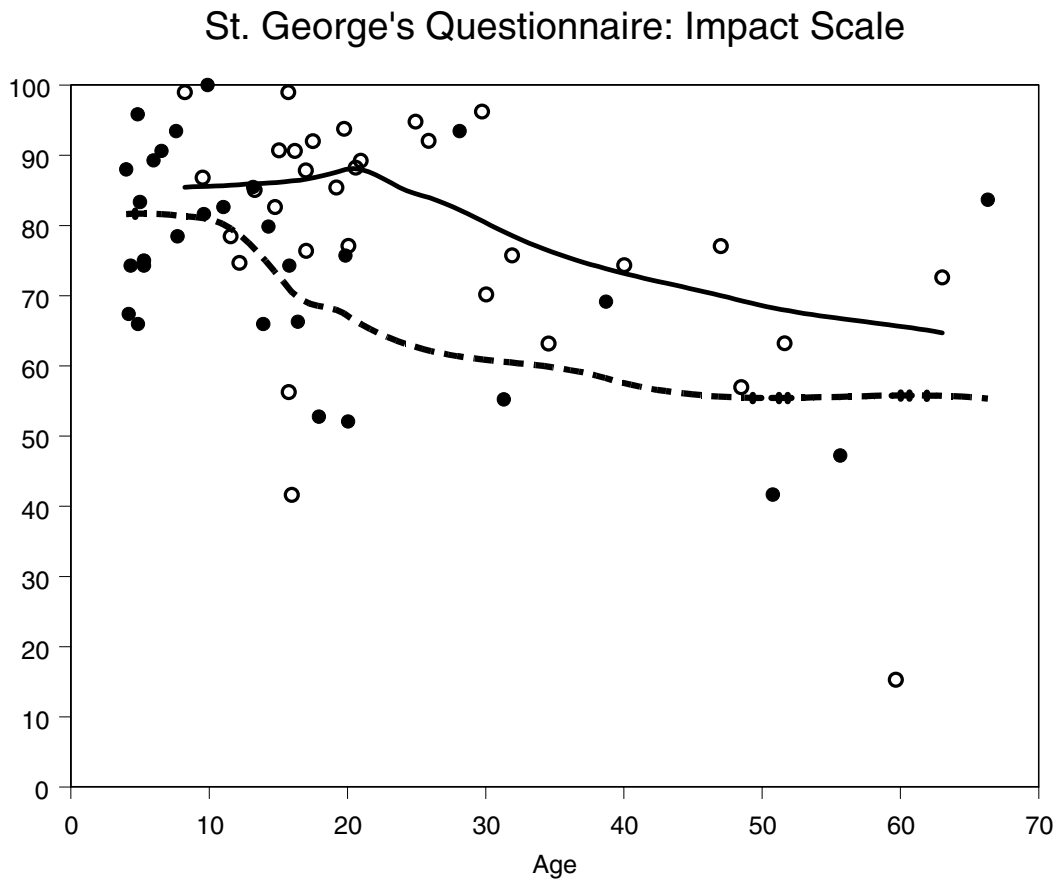

Figure 5
The Impact scale of the St. George's Respiratory Questionnaire plotted in relation to the age of the respondent and the time since diagnosis (calculated as Current Age minus Age at diagnosis). Individuals with a time since diagnosis of more than eight years are shown as solid black circles (•), and the lowess curve is shown as a solid black line (**-**), and those with a time since diagnosis of less than eight years are shown as open black circles (❍) and the lowess curve is shown as a dashed black line (- - - -).

ceased after diagnosis. The effect of time since diagnosis upon the SGRQ **Impact** Score is shown in figure 5, a median split being used to group the patients into those who have been diagnosed for more than eight years (mean time since diagnosis = 4.5 years, SD= 2.1; mean age = 17.2, SD = 16.5) and those who have been diagnosed less than eight years (mean time since diagnosis = 15.3 years, SD = 8.9; mean age = 25.4, SD = 14.8) . The SGRQ **Activity** score shows an effect that is almost significant at the .05 level (p = .085), and the effect is in the expected direction (a positive regression coefficient on time since diagnosis). If a one-tailed test has been used, which seems reasonable since treatment is expected to benefit symptoms, then the effect would have reached the conventional level of significance (p = .042).

PCD-SI compared with PCD-SS

Iindividuals with PCD-SI and those with PCD-SS were compared on the various measures of symptoms and health status. Simple t-tests showed no differences between PCD-SI and PCD-SS, and neither were there effects of *situs* on symptoms after taking age into account using a multiple regression. A detailed table of results is available from the first author on request.

Other symptoms

Patients with PCD often report a range of other symptoms including nasal congestion, headache, earache, sinus pain, sore throat, and heartburn [4,38]. We assessed each of these by modifying one of the questions of the SGRQ. Respondents indicated the extent to which the problem

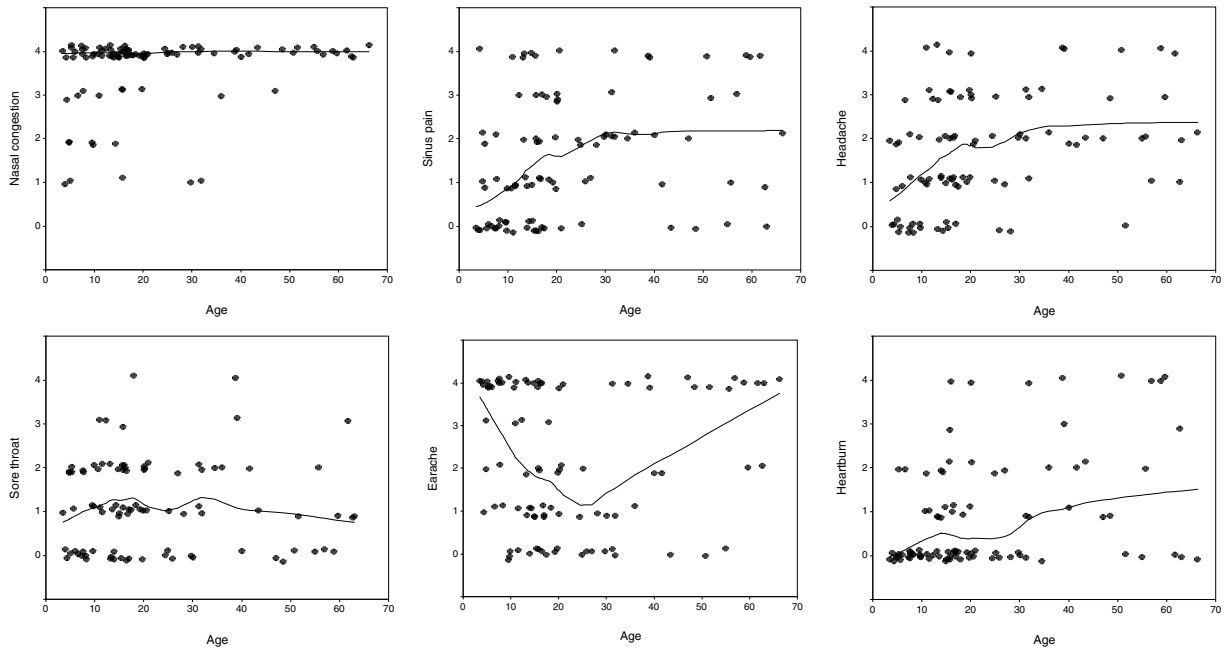

Figure 6
Nasal congestion, sinus pain, headache, sore throat, earache and heartburn in relation to age. Symptoms are scored on a scale of 0 (None) to 4 (almost every day) – see text. A small amount of vertical jitter has been added to data points so that individuals are more easily distinguishable. The solid lines are lowess curves.

had affected them *over the past four weeks*, using five categories: 'Not at all' [scored 0], 'One day or so' [Scored 1], 'A few days a month' [Scored 2]. 'Several days a week' [Scored 3], or 'Almost everyday' [Scored 4]. Figure 6 shows that almost all individuals reported "a runny nose and nasal congestion". "Pain over my sinuses" and "headaches" typically affected patients for a few days a month, whereas "a sore throat" and "indigestion of heartburn (reflux)" affected patients once a month or so. There was a tendency for sinus pain, headache and heartburn to increase with age. "Earache or hearing problems" showed a more unusual pattern, being very frequent in childhood and declining through adolescence to a minimum at about 25 years of age, and then climbing once more in frequency. The 'U'-shaped shape of the age curve for earache is confirmed using multiple regression by a highly significant quadratic effect of age after taking the linear effect into account ($p < .001$).

Treatments

Although our study did not have access to clinical records, we did ask a number of questions about the treatments that patients used "to help with the symptoms of PCD". Table 2 summarises the results. A clear majority of patients, although not all, were currently using physiotherapy and breathing exercises/techniques, and about half were taking regular antibiotics and bronchodilators. The use of expectorants and antacids or other drugs to help with heartburn or reflux were more common with increasing age. None of the treatments seemed to be used more commonly in patients who had been diagnosed longer ago.

Table 2: Treatments used by patients in the study, and the Pearson correlation with age, age at diagnosis and years since diagnosis with usage (scored 3 = 'At present', 2 = 'In the past' and 1 = 'Never used').

	Usage			Correlation of usage with:		
	"Never used"	"In the past"	"At present"	Age	Age at diagnosis	Years since diagnosis
Regular antibiotics	10 (11%)	36 (39%)	46 (50%)	.042 (NS)	.227 (NS)	.236 (NS)
Bronchodilators (inhaler or tablets)	15 (17%)	23 (25%)	53 (58%)	.166 (NS)	.122 (NS)	.008 (NS)
Mucolytics to thin the sputum	75 (89%)	6 (7%)	3 (4%)	.029 (NS)	.092 (NS)	-.046 (NS)
Physiotherapy	1 (1%)	21 (23%)	69 (76%)	-.139 (NS)	-.022 (NS)	-.174 (NS)
Breathing exercises and techniques	11(12%)	13 (14%)	68 (74%)	.119 (NS)	.228 (NS)	-.120 (NS)
Expectorants	64 (73%)	19 (22%)	5 (6%)	.409 (p < .001)	.420 (p = .001)	.176 (NS)
Antacids or other drugs for heartburn or reflux	64 (72%)	16 (18%)	9 (10%)	.380 (p < .001)	.398 (p = .002)	.101 (NS)

An important question concerns the relationship between treatment usage and symptoms. We therefore carried out a regression analysis relating symptom measures to the seven treatments about which we had asked. At the first step, age and years since diagnosis were entered into the analysis, and then a forward entry stepwise process was used to examine the predictive effects of the therapies. The SGRQ **Symptoms** score was predicted firstly by Antacids/ Heartburn-Reflux treatments (beta = -.445, p < .001), and then by use of bronchodilators (beta = -.275, p = .012). Given the scoring of the treatment measures (high scores indicate treatment use), and the scoring of the symptom measures (low scores indicate poorer functioning), the negative beta coefficients indicate that those taking the treatments have lower symptom scores than those not taking them. Broadly similar results were found for the other outcome measures. The SGRQ **Activity** score was predicted firstly by Antacid use (beta = -.469, p < .001), and then by expectorant use (beta = -.323, p = 016). The SGRQ **Impact** score was predicted firstly by expectorant use (beta = -.450, p < .01), and then by Antacid use (beta = -.301, p = .010). The SF-36 Physical Components Score was predicted firstly by Expectorant use (beta = -.461, p = .001), and then by Antacid use (beta = -.296, p = .024). Finally, the SF-36 Mental Component Score was predicted only by Antibiotic use (beta = -.283, p = .037). Mucolytic use, physiotherapy and breathing exercises were not predictive of any of the symptom scores after other treatments had been taken into account. It should be noted that in each of the analyses the beta coefficient is negative, meaning that those taking the treatment had *poorer* health.

Discussion

Primary Ciliary Dyskinesia is a chronic illness, in which, as Siewert emphasised in his description of the first properly documented case, symptoms can be present from soon after birth. Although the symptoms even from birth are inconvenient, our results suggest that during childhood and adolescence there is relatively little impact upon normal, healthy functioning, the standard measures of the SF-36 showing little deviation from normality. However during the mid-20s there is a continual and progressive increase in respiratory symptoms. Our results using the St. George's Respiratory Questionnaire, which has been validated against objective measures of respiratory function [32-34] are clearly parallel to the decline in respiratory function with age which was measured by Ellerman and Bisgaard [28] using standard spirometric techniques. A replotting of those data (available from the first author), clearly shows a graph which is parallel in form to that of our figure 5. The long-term, longitudinal study of Ellerman and Bisgaard [28] also showed that respiratory function was significantly worse in patients who presented in adulthood rather than when the condition was diagnosed in childhood. As in our results, Ellerman and Bisgaard [28] also showed that there was little deterioration once patients were under the supervision of a respiratory clinic, when management included regular spirometry, daily physiotherapy and monthly sputum cultures.

As well as lower respiratory symptoms, individuals with PCD also suffer a range of other symptoms from the ears, nose and throat, and upper gastrointestinal tract. Of some interest in our study is the decline in earache through adolescence, which provides a useful validation of the

quality of our data, since such problems are thought to resolve as the Eustachian tube becomes larger due to growth. The subsequent resurgence of earache was more surprising, and requires further exploration.

On the physical scores of the SF-36 in our study there is a continual decline with age, such that from about the age of 40 onwards the health status of these individuals is one to one and a half standard deviations below the population mean (although there is substantial variability at all ages). That is a large and important effect on health, and although PCD does not usually manifest in an increased mortality, there is clearly a moderate degree of morbidity which affects normal physical functioning (although there seems relatively little effect on social and emotional functioning beyond the normal effects of ageing).

The results, particularly those shown in figure 3, are important because they suggest that the morbidity resulting from PCD is progressive across the life-span, and hence that early therapeutic interventions may be able to prevent the deterioration in health that we have found. The possible benefit of early medical intervention, particularly on the **Impact** and **Activity** scores of the SGRQ, is suggested by the analyses of table 1, which show that an earlier diagnosis, which results in more years of treatment since diagnosis, has a positive impact on symptoms. There is a need for properly designed, prospective studies both of early diagnosis itself, and of interventions such as regular sputum culture, routine use of antibiotics, and physiotherapy, all which may reduce morbidity [4].

Although earlier diagnosis may contribute to a better clinical outcome, it is not clear from our data what is the main causative component of that better outcome. We had basic self-report measures of the treatments received by these patients, and we looked for correlations with outcome. Although they were present and highly significant, in each case the regression coefficients were negative, meaning that those taking the treatments had poorer health. The implication is that the treatments taken are a response to symptoms, rather than that they are having a positive impact upon them. That is supported by the majority of the significant effects concerning expectorants and antacids (which are readily available as non-prescription medicines) rather than antibiotics, bronchodilators, or physiotherapy and breathing exercises, which are more associated with hospital treatment. That interpretation is supported by the sole correlate of antibiotic use being with the SF-36 Mental Component Score, suggesting antibiotics can be a response to anxiety and other psychological responses by patients to their illness.

Our data represent the largest published study of the symptoms and effects upon health in PCD, but we are aware that there is a risk that our sample may be biassed. All of the subjects are volunteers who had chosen to join the PCD Family Support Group, so that it is possible either that our subjects are not representative, perhaps coming from the more severe end of the spectrum of disease, or, particularly in the younger patients, their condition is less severe but parents have chosen to be involved in the support group in order to have as much information as possible about the condition. Although both biasses are possible, they also emphasise the need for properly representative and systematic studies of patients who are typical of the entire population. That would also require a concerted effort to identify a national sample of all individuals with PCD, independent of symptoms and presentation and diagnosis at clinics.

Many of the subjects in our study are relatively young, in part reflecting the frequent presentation of patients due to symptoms in the neonatal period, and the increased awareness of paediatricians for the diagnosis in young patients with chronic respiratory or otolaryngological problems. We encouraged parents to respond on behalf of their children and with the collaboration of their children, and were gratified by the response rate. Although there might be a concern, particularly in children under the age of ten, that the reports are not reliable, the fact of the matter is that those under ten report similar patterns of symptoms to those in their teens, and that this provides support and validation of the younger patients' responses. It is also the case that none of our conclusions would differ if individuals under the age of ten or twelve or sixteen were eliminated from this report.

A striking, and biologically fascinating, aspect of PCD is that half of the patients have *situs inversus* (and Siewert himself was himself impressed by the co-occurrence of the unusual conditions of bronchiectasis in childhood and *situs inversus*). Although it might be expected that the age at diagnosis would be lower in individuals who had *situs inversus* (PCD-SI) than in those with *situs solitus* (PCD-SS) the trend in this study did not reach statistical significance. The present results are therefore similar to those of Coren *et al* [38] who also found a non-significant trend towards PCD-SI cases being diagnosed earlier than PCD-SS. Even if a larger series were to find a significant effect, the broad conclusion has to be that even if the diagnosis is often triggered by the presence of *situs inversus*, the existence of other symptoms, in particular bronchiectasis in younger patients, should be sufficient to suggest PCD as a possible diagnosis.

Although only a half of PCD patients have *situs inversus*, the rest having the so-called 'partial Kartagener's syndrome', our analysis makes clear that the symptoms of PCD-SI and PCD-SS are the same, and the evolution of the

condition with age is also the same. The situs inversus that occurs is therefore independent of the chronic respiratory symptoms, and therefore the true syndrome, as Afzelius and others [5] have recognised, is upper and lower respiratory tract problems due to ciliary immotility, coupled with *random situs*.

Competing interests

None declared.

Acknowledgments

We are grateful to Carol Polak and the members and the scientific committee of the PCD Family Support Group for their help with this research, and to Andrew Bush and Mark Gardiner for helpful discussions.

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Pre-publication history

The pre-publication history for this paper can be accessed here:

http://www.biomedcentral.com/1471-2466/3/4/prepub