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Factors influencing age at diagnosis of primary ciliary dyskinesia in European children

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ABSTRACT

Primary ciliary dyskinesia (PCD) is a hereditary disorder of mucociliary clearance causing chronic upper and lower airways disease. We determined the number of patients with diagnosed PCD across Europe, described age at diagnosis and determined risk factors for late diagnosis.

Centres treating children with PCD in Europe answered questionnaires and provided patients' anonymous lists.

In total, 223 centres from 26 countries reported 1009 patients aged <20 years. Reported cases/million children (for 5-14 year olds) were highest in Cyprus (111), Switzerland (47) and Denmark (46). Overall, 57% were males and 48% had *situs inversus*. Median age at diagnosis was 5.3 years, lower in children with *situs inversus* (3.5 vs. 5.8 years, p<0.001) and in children treated in large centres (4.1 *vs.* 4.8 yrs, p=0.002). Adjusted age at diagnosis was 5.0 years in Western Europe, 4.8 in the British Isles, 5.5 in Northern, 6.8 in Eastern and 6.5 in Southern Europe (p<0.001). This strongly correlated with general government expenditures on health (p<0.001).

This European survey suggests that PCD in children is under-diagnosed and diagnosed late, particularly in countries with low health expenditures. Prospective studies should assess the impact this delay might have on patients' prognosis and on health economic costs across Europe.

Keywords
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INTRODUCTION

Primary ciliary dyskinesia (PCD) is a clinically and genetically heterogeneous group of hereditary disorders characterised by abnormal ciliary beat pattern, often with a low beat frequency and mostly, although not always, detectable ciliary ultra-structural abnormalities.[1-7]

The main consequence is the impairment of mucociliary clearance from upper and lower airways leading to chronic airway infection and inflammation. The diagnosis should be suspected in children with chronic rhinitis and a chronic wet sounding cough, most frequently from birth. Approximately 40-50% of affected children have *situs inversus*. The combination of *situs inversus*, bronchiectasis and sinusitis has been referred to as Kartagener syndrome. Other disease manifestations associated with PCD are caused by altered motility of cilia/flagellae of distinct cell types, including male infertility (sperm tail), hydrocephalus (ependymal cilia) and complex heart disease (nodal cilia).[8]

There are no representative international data on prevalence, age at diagnosis, burden of disease and prognosis in PCD patients. Available information comes from case series in single countries, the largest consisting of 55 and 78 patients from the UK and the US respectively.[4, 9] Reported prevalence shows large variations with estimates between 1 in 2,200 and 1 in 40,000, using different approaches.[10-13] Although early diagnosis is thought to reduce long-term pulmonary morbidity and prevent unnecessary investigations and unhelpful treatments, there is evidence suggesting that diagnosis is often delayed primarily due to lack of awareness and difficulties in establishing the diagnosis.[9]

The European Respiratory Society (ERS) task force on PCD in children recently published a consensus statement, which highlighted the poor evidence base on epidemiology, diagnosis and treatment of PCD in children.[14] To collect baseline data on the situation in Europe and increase awareness of the condition, the taskforce then performed an international survey. The aims of the survey were to provide basic data on numbers and characteristics of paediatric PCD patients in Europe, to describe age at diagnosis and to determine factors associated with delayed diagnosis. This should inform the European wide health care agenda for these patients.

METHODS

Study design and population

Using a two-stage design, we performed a cross-sectional questionnaire survey of all institutions (tertiary, secondary or primary care centres) considered likely to be treating paediatric PCD patients in Europe. With the help of the ERS membership roster, we aimed to identify in each country a national representative who distributed the questionnaires to all such centres. Thanks to repeated efforts, we found a national representative in most, but not all countries in Europe. Turkey and Israel, who volunteered, were also included. Questionnaires were mailed between January 2007 and October 2008 and replies were collected until January 31, 2009. Depending on the national health care organisation, some representatives contacted only tertiary care centres while others included smaller institutions.

Data on total population counts for each participating country, stratified by 5-year age groups, were obtained from the U.S. Census Bureau International Data Base for 2007.[15] Participating countries were grouped into five regions according to the United Nations (UN) definition of the European regions, with the following exceptions: The United Kingdom (UK) and Ireland were analysed as a separate region (British Isles). Estonia, Israel, Serbia and Turkey were grouped with Eastern Europe.[16]

Data on general government expenditure on health (GGHE, the sum of outlays for health maintenance, restoration or enhancement paid for in cash or supplied in kind by government entities) were obtained from WHOSIS, the WHO Statistical Information System database bringing together core health statistics for the 193 WHO member states.[17]

Questionnaire

The ERS task force developed a short questionnaire for national representatives, and a detailed questionnaire for clinical centres. National representatives reported the number of tertiary care paediatric centres in the country and listed all centres receiving a questionnaire. Tertiary care centres were defined as university hospitals or other tertiary referral centres, secondary care centres as regional referral centres with a respiratory unit and primary care centres as paediatric practices or small hospitals.

In a separate questionnaire, we asked each centre to supply a list of patients currently followed up, with dates of birth, dates of diagnosis, sex and information on *situs inversus*. For reasons of patient confidentiality, no identifying data were collected. To limit work for collaborating centres, no clinical details such as method of diagnosis or treatments, pedigrees or genetic data were collected at this stage.

Analysis

We double-entered all questionnaires into an EpiData database, eliminated double counts of cases reported by more than one centre, and analysed the data using Stata statistical software (version 10, STATA Corporation, College Station, TX). Cases reported by both a tertiary care centre and a smaller centre were attributed to the tertiary care centre. To ensure comparability between countries, response rate was calculated as number of paediatric tertiary care centres replying / number of tertiary care centres existing in this country. The number of reported PCD cases in five-year age bands was compared to total population counts in the same age band.

For comparing numbers of diagnosed cases of PCD between countries, we concentrated on children aged 5-14 years at the time of the survey, because the upper age range of patients in paediatric care varied. For the other analyses, we included all patients aged <20 years at time of the survey. Age at diagnosis being positively skewed, medians and geometric means are reported rather than means, and data were log-transformed for analysis. To determine risk factors for a delayed diagnosis, we used univariable and multivariable linear regression. All factors associated with the outcome ($p<0.05$) and gender were retained in the multivariable model. In a sensitivity analysis, all computations were repeated for countries with a response rate above 60%.

RESULTS

Response rates and numbers of centres treating PCD patients

We received 223 centre questionnaires from 26 countries (**Table 1**). A list of patients was completed by 194 centres (141 tertiary and 53 secondary or primary care centres). Small centres often returned the questionnaire, filling in information on their diagnostic approaches for suspected PCD, but without adding a patient list, because they referred their PCD patients to a tertiary care centre for further care. From tertiary care centres, the overall response rate was 52% (141/272), varying between countries from 18% to 100%. Clearly, in countries with a low response rate of tertiary care centres, the reported lists of patients do not represent the true prevalence of PCD in this country, and not even the number of diagnosed cases. However, in countries with a 100% response rate of tertiary care centres, the reported patients might be a fair estimate of paediatric patients diagnosed in this country. To facilitate interpretation of results, these are therefore reported stratified by country and sorted by response rates, with subtotals summarising results for countries with a high response rate.

Numbers of doctor-diagnosed PCD patients per country

The centres reported individual-level data on 1192 cases (**Table 2**). Of these, 1009 were aged <20 years at the time of the survey. Numbers of reported patients differed by age: at the time of the survey 161/1009 patients (16%) were aged 0-4 years, 311 (31%) 5-9 years, 320 (32%) 10-14 years, and 217 (21%) 15-19 years. An additional 178 patients were aged ≥20 years (**Figure 1**). For 5 children information on age was missing. In the 13 countries also distributing questionnaires to smaller centres, 15% of cases (108/721 patients) came from non-tertiary centres. The age distribution varied between countries, with more young patients reported from Austria, Germany and Italy, and older children from Hungary, Cyprus, Denmark, and Sweden (**Figure 2**).

To estimate the prevalence of diagnosed PCD patients per country, we compared numbers of reported patients aged 5-14 years to numbers of inhabitants aged 5-14 years in the respective country. We found large international differences, with highest frequencies in Cyprus (111 cases/million inhabitants, equivalent to 1/10,000 children), Denmark (46/million) and Switzerland (47/million, both approximately 1/20,000 children; **Table 2** and **Figure 3**).

Characteristics of diagnosed PCD patients

Current age was reported for 1187 cases and ranged from 0 to 68.5 years (**Figure 1**). Median age (interquartile range, IQR) was 11.8 (7.3-16.8) years. There was a gender

difference with 573 of 1009 patients diagnosed between age 0-19 years being males (57%, 95% CI 54-60%) and 430 females (43% (40-46%); **Table 3**).

Overall, 437 children (44% (95% CI 41-47%)) had *situs inversus* (**Table 3**). When excluding the outlier Spain (which reported only 10% with *situs inversus*) this proportion rose to 48% (427/892). The proportion of patients with *situs inversus* was not associated with use of diagnostic tests (e.g. biopsy of ciliated epithelium p=0.08, ciliary beat frequency and pattern p=0.92, electron microscopy p=0.22) in the respective countries, nor with number of reported cases (p=0.96, data not shown).

Age at diagnosis

Age at diagnosis was reported for 1051 patients. Of these, 473 (45%) had been diagnosed at an age of 0-4 years, 319 (30%) aged 5-9, 155 (15%) aged 10-14, 52 (5%) aged 15-19, and 52 (5%) aged 20 years or more. Among these, 897 were currently younger than 20 years and included in further analyses. The distribution of age at diagnosis had two peaks: a first narrow and high peak between 0-2 years, mainly accounted for by children with *situs inversus* but also visible in those without (**Figures 4a** and **4b**). This was followed by a second, broader peak extending from age 4-8 years, with a long tail thereafter. This second peak was more pronounced in children with *situs solitus*. Only 9% (95% CI 7-11%) of children were diagnosed in the neonatal period, 16% (12-19%) of those with *situs inversus*, and 4% (2-6%) of those without (p<0.001).

Median age at diagnosis was 5.3 years (IQR 1.2-8.2, range 0 to 19), lower in children with *situs inversus* compared to those without (3.5 *vs.* 5.8 years, p<0.001), and in children treated in large centres (>20 PCD patients) compared to smaller ones (4.1 *vs.* 4.8 years, p=0.002) (**Table 4**). Adjusting for current age, sex, *situs inversus*, and size of centre, the average age at diagnosis (years, geometric mean) was 5.0 in Western Europe, 4.8 in the British Isles, 6.5 in Southern, 5.5 in Northern and 6.8 in Eastern Europe (p<0.001, **Table 4**). Results were similar when the analysis was repeated for countries with a response rate >60% (online supplement **Table E1**). Adjusted age at diagnosis for individual countries is shown in **Figure E1** (online supplement).

Mean age at diagnosis in different countries was strongly correlated with GGHE in the respective country (**Figure 5a**): a 1000 US dollar increase in GGHE was associated with a 0.60 years decrease in age of diagnosis (95% CI 0.55-0.65, p<0.001). Similarly, the prevalence of diagnosed cases was correlated with GGHE (**Figure 5b**), with an increase of 5.23 (4.62-5.84, p<0.001) diagnosed cases per million inhabitants aged 5-14 years per 1000 US dollar increase in GGHE. Again, results were similar for countries with a response rate

>60%. Inclusion of the outlier Cyprus changed the estimate to 3.11 (2.14-4.10, p<0.001) diagnosed patients per million inhabitants per 1000 US dollar increase (**Figure E2b** online supplement). In Cyprus, age at diagnosis was mainly defined by the starting date of a paediatric respiratory clinic, which actively searched for cases. There was no correlation between mean age at diagnosis in a country and estimated prevalence of PCD (rho=-0.018, p=0.59), suggesting again that our findings for age at diagnosis were not affected by response rates to the survey.

DISCUSSION

This paper presents the largest international survey of paediatric PCD patients ever undertaken, and includes data from 1192 patients from 26 European countries. In countries with a good response rate, prevalence of diagnosed cases in 5-14 year-olds was between 1/10,000 and 1/20,000. Median age at diagnosis was 5.0 years, lower in those with *situs inversus* and in children treated in large centres and varied significantly between regions. Both number of diagnosed cases and median age at diagnosis were strongly correlated with the general government expenditure on health.

Strengths and limitations

This is the first study assessing numbers of doctor-diagnosed PCD cases in children in an international survey with a uniform methodology. Only one study exists where the same diagnostic methodology was used to determine the prevalence of PCD in a well defined population. This showed a very high incidence of 1 in 2,2000 in a British Asian population that may have been due to high levels of consanguinity.[13] Other approaches were limited to single countries [10] or specific populations such as atom bomb survivors,[11] or used approximation methods based on radiologically confirmed bronchiectasis.[12] Our approach has its own limitations: response rates varied between countries, diagnostic criteria differed, some centres did not list all patients, only paediatricians were approached and undiagnosed patients could obviously not be included. Age at diagnosis was missing for 11% of patients. A few countries did not participate. For these reasons results were stratified by country and compared to national response rates.

To keep the workload for participating centres manageable we collected only limited information on individual patients. Therefore, our data essentially represent “doctor-diagnosed PCD” and we cannot be certain if individual patients had been diagnosed according to current diagnostic standards (ciliary beat frequency and pattern, electron microscopy, cell culture, other specific tests),[1] or mainly on clinical grounds (symptoms, bronchiectasis and *situs inversus*). Hence, some of the cases reported in this survey might not suffer from PCD. For example, only a proportion of patients with *situs inversus* have PCD and we are aware of a number of patients diagnosed initially on clinical grounds with PCD whose diagnosis had to be revised when appropriate diagnostic tests were conducted. However, 94% of centres reporting patients had electron microscopy or ciliary function tests available, and excluding the other 6% in a sensitivity analysis did not change any of the main results. It would have been ideal to narrow this down further by only including data from centres which assessed both function (ciliary beat frequency and pattern) and structure (transmission electron microscopy, but this would have reduced the sample size greatly. All

the countries with high prevalence estimates (Cyprus, Denmark, Switzerland) have facilities for a detailed work-up. In Switzerland, every PCD patient must be biopsied for coverage of medical costs by the insurance for birth defects. In Cyprus and Denmark, all PCD patients were diagnosed in an experienced single national reference centre employing up-to-date diagnostic methods.

Numbers of diagnosed cases per country

The reported numbers of children with doctor-diagnosed PCD varied widely between countries. Bearing in mind the differences in prevalence of cystic fibrosis across Europe, it is not impossible that part of this variability reflects true differences in disease incidence e.g. underlying geographic differences in mutational data, founder effects for certain gene mutations or differing proportions of couples with consanguineous marriages.[18] Unfortunately, ethnicity and country of origin for immigrant patients could not be assessed in this survey. However, we believe that varying response rates and differences in awareness and diagnostic work-up of PCD between participating countries are by far the most important factors explaining differences in reported numbers of patients and in prevalence estimates.

In several large countries (France, Italy, Germany, UK) response rates of tertiary care paediatric hospitals were low and sometimes (e.g. the Netherlands, Slovakia and the UK), participating centres reported only a fraction of their patients. Also, patients treated by adult pulmonologists or ear, nose and throat (ENT) physicians might have been missed. For an approximation of the prevalence of diagnosed PCD in children, we have to rely therefore on data from countries with high response rates, mainly those treating all patients in national reference centres (Cyprus, Denmark) and small countries with few and closely collaborating paediatric pulmonologists (Austria, Switzerland).

As the methods of diagnosis were not ascertained for individual patients, it is possible that PCD was over- or under-diagnosed in some places. Over-diagnosis could be suspected in countries with a low proportion of children with *situs inversus*. Our results do not support this. Overall, there was no correlation between the proportion with *situs inversus* in a country and the prevalence of diagnosed cases ($p=0.96$), and countries with a high prevalence often reported a high proportion of *situs inversus* (Switzerland: 56%; Austria: 53%; Cyprus: 45%). Under-diagnosis is probably more of an issue. For instance, a PCD variant caused by recessive *DNAH11* mutations is characterised only by a subtle alteration of the ciliary beat recognisable only by high-speed videomicroscopy, without ultrastructural axonemal defects. Most of these cases will have been missed in our study, because only few centres used high-speed videomicroscopy analyses.[7, 19, 20]

Balancing all these factors in mind, and considering that there are likely undiagnosed children with minor symptoms, we believe that the often cited prevalence estimates of 1/30,000 to 1/40,000 are too low.[10, 12] All countries in our survey with higher estimates (Cyprus (1/10,000), Denmark and Switzerland (both 1/20,000)) use a thorough diagnostic work-up based on nasal/bronchial biopsies, electron microscopy and ciliary beat analysis and well-organised care in one or few specialised centres, making over-diagnosis unlikely. Clearly, comprehensive national PCD registries that record baseline and follow-up data on all cases diagnosed in a country are needed to derive more valid prevalence estimates.

Characteristics of reported patients

Numbers of reported patients per age group increased with age from infancy to age 8-10 years, and decreased thereafter (Figure 1). While the increase in early childhood is probably explained by delays in diagnosis, the decreasing numbers of older children might reflect early transition into adult care or improved diagnosis in more recent cohorts of children, or both.

Situs inversus was reported in 48% (45-51%) of patients (excluding Spain). This proportion is slightly lower than 50%, which might be explained by the fact that central microtubular defects, responsible for some PCD cases, are not associated with *situs inversus.* In fact, our results are identical to those reported by Kennedy et al in his large sample of patients worked up in great detail (47.7% with *situs inversus*),[21] implying that overall, the quality of diagnosis in our survey might be satisfactory.

The sex distribution was unequal, with a higher proportion of boys (57%, 95% CI 54-60%) in all age groups. We can only speculate on the underlying causes: boys might have a more typical disease presentation due to their known proneness to respiratory infections,[22] or girls might be under-diagnosed compared to boys even when presenting with similar symptoms, the so-called Yentl syndrome.[23] Perhaps X chromosomal recessively inherited PCD variants may also contribute to the unequal sex distribution. This has been shown for X-linked syndromic PCD variants caused by *RPGR* (PCD + retinitis pigmentosa) and *OFD1* (PCD + mental retardation) mutations that are responsible for PCD variants associated with retinitis pigmentosa.[24-26] Possibly, other non-syndromic PCD variants are also caused by mutations of genes located on the X chromosome.

Age at diagnosis

As previously reported, age at diagnosis was nearly twice as high in children with *situs solitus*.[9] Although overall more PCD cases were reported among males, age at diagnosis did not vary by sex.

Size of the treating centre was strongly associated with age at diagnosis. Children were diagnosed at a younger age in centres caring for >20 PCD patients compared to smaller centres (4.1 *vs.* 4.8 years, p=0.002). This suggests that, analogous to CF, it might be advisable to centralise care for PCD patients in a few highly specialised centres. Therefore, it is of concern that in many countries, PCD patients were treated by a large number of centres. For instance in Switzerland 65 patients were reported by 17 centres (8 tertiary care, 9 others). Similarly, in the UK, patients were reported by 32 centres (18 tertiary, 14 others).

Adjusting for current age, sex and *situs inversus*, we found considerable international differences in age at diagnosis, with earlier diagnosis in the British Isles, Northern and Western Europe, compared to Southern and Eastern Europe. This was partly explained by differences in the general government expenditures on health, with a 0.6 years decrease in age at diagnosis for every 1000 US dollar increase in GGHE.

Implications and conclusions

Little is known on the impact of a delayed or missed diagnosis on patients. Adult patients have a high burden of chronic respiratory morbidity.[4] Several studies showed reduced lung function in older patients.[27, 28] It has been reported that lung function may be stabilised after diagnosis and appropriate management, suggesting a positive effect of early diagnosis and appropriate respiratory management on long-term outcome of PCD patients.[4, 27] However this was not confirmed in a recent analysis of data from Denmark, and further large prospective studies are needed.[28] The next step in this collaboration will be to extend our database and use it as a starting point for an international study collecting detailed information on diagnosis, clinical presentation and measurements in a representative sample of patients, with the objective of describing morbidity and burden of disease in paediatric PCD, particularly signs of irreversible damage (such as bronchiectasis). Comparison of children diagnosed early to those diagnosed at a later age will allow the estimation of the economic burden of delayed diagnosis. For CF it has been shown that early diagnosis by newborn screening saves money by reducing the costs of treatment;[29] we speculate that this might also apply to PCD. Long-term prospective follow-up of these patients will allow assessment of prognosis and response to treatments. Finally, the use of appropriate databases will allow the performance of randomised controlled trials of treatment. As recently highlighted in European consensus statement [14] an evidence base for the treatment of PCD is still lacking.

In conclusion, this study strongly suggests that PCD is more frequent than generally thought, but under-diagnosed and diagnosed late in many European countries. Pre-requisites for improving diagnostic rates include a greater clinical awareness of the condition. Indications for testing for PCD include: children with situs inversus or heterotaxy, children with chronic

productive cough or bronchiectasis of unknown cause or severe upper respiratory morbidity, children with cerebral ventriculomegaly, siblings of patients, babies with unexplained neonatal respiratory distress, males with immotile sperm and females with recurrent ectopic pregnancy.[14] Diagnostic testing for PCD and interpretation of results are difficult and involve ciliary beat pattern and frequency analysis using video recording and electron microscopy as key techniques, accompanied in some cases by genetic testing. Sometimes repeated brush samples and culture of ciliary brushings are necessary.[14] Our study strongly suggests that centralised evaluation and treatment of children with PCD at one or few respiratory references centres in each country is associated with more and earlier diagnoses, and highlights the inequalities in the diagnosis of PCD across Europe. These inequalities are partly explained by insufficient government funding for health and might be an appropriate subject for the European Union to address.

Table 1: European survey on PCD in children: country totals for returned questionnaires and response rates in tertiary care paediatric centres

Country	Questionnaires received			National response rate (only tertiary care centres) ‡
	Total *	Centres listing cases†		
		Tertiary care centres	Other	
Austria	13	5	6	100.0
Cyprus	5	1	0	100.0
Denmark	1	1	0	100.0
Hungary	1	1	0	100.0
Slovakia	1	1	0	100.0
Switzerland	19	8	9	100.0
Greece	5	5	0	83.3
Finland	4	4	0	80.0
Israel	8	7	1	77.8
Netherlands	7	6	1	75.0
Portugal	4	3	1	75.0
Spain	24	17	1	68.0
Belgium	8	5	2	62.5
France	6	5	1	62.5
Subtotal ¶	**106**	**69**	**22**	**76.7**
United-Kingdom	34	18	14	56.3
Italy	19	15	4	55.6
Sweden	16	5	9	55.6
Estonia	2	1	0	50.0
Serbia	2	1	1	50.0
Czech Republic	2	2	0	40.0
Romania	3	3	0	33.3
Turkey	14	12	0	32.4
Bulgaria	2	1	0	25.0
Germany	19	10	3	18.2
Ireland	1	1	0	-
Norway	3	3	0	-
Total	**223**	**141**	**53**	**51.8**

* all questionnaires that were returned completed; †all questionnaires that contained a list of patients; ‡ calculated as the number of questionnaires returned by tertiary care paediatric centres, divided by the total number of tertiary care paediatric centres in the respective country; ¶ the subtotal summarises results for all countries with a response rate of >60%

Table 2: Number of reported cases and estimated prevalence of diagnosed PCD in children

Country	Patients reported * (n)			Population count (2007)	Estimated prevalence of diagnosed cases per million inhabitants
	total	0-19 yrs	5-14 yrs	5-14 yrs	5-14 yrs
Austria	47	36	21	871751	24.1
Cyprus	27	20	12	108149	111.0
Denmark	95	51	32	700559	45.7
Hungary	43	35	18	1042915	17.3
Slovakia	7	7	2	606167	3.3
Switzerland	65	62	40	844638	47.4
Greece	20	20	15	1017416	14.7
Finland	4	4	3	607701	4.9
Israel	87	62	31	1261179	24.6
Netherlands	6	6	6	2013275	3.0
Portugal	7	6	6	1178035	5.1
Spain	120	104	78	3806288	20.5
Belgium	22	17	8	1164904	6.9
France	103	97	68	7799205	8.7
Subtotal †	**653**	**527**	**340**	**23022182**	**14.8**
United-Kingdom	82	81	52	7184605	7.2
Italy	173	128	70	5401122	13.0
Sweden	49	48	26	1007512	25.8
Estonia	1	0	0	131574	0.0
Serbia	16	16	10	1276736	7.8
Czech Republic	13	13	4	974518	4.1
Romania	8	8	3	2323649	1.3
Turkey	105	102	65	12090479	5.4
Bulgaria	-	-	-	670619	-
Germany	63	58	39	7995913	4.9
Ireland	-	-	-	562709	-
Norway	29	28	22	609275	36.1
Total	**1192**	**1009**	**631**	**63250893**	**10.0**

* number of patients listed individually with date of birth and sex; † the subtotal summarises results for all countries with a response rate of >60%

Table 3: Characteristics of diagnosed PCD patients aged 0-19 years at time of the survey (n=1009)

Country		Female sex		*Situs inversus*		Age at diagnosis (years) *		
	n total *	%	95% CI	%	95% CI	n total	median	IQR
Austria	36	42	[25-59]	53	[36-70]	28	4.8	[0.3-8.2]
Cyprus	20	40	[16-64]	45	[21-69]	19	10.1	[7.0-13.9]
Denmark	51	45	[31-59]	35	[22-49]	51	4.1	[0.8-7.9]
Hungary	35	31	[15-48]	34	[18-51]	35	5.5	[4.2-8.3]
Slovakia	7	43	[0-92]	100	-	7	2.6	[1.8-10.3]
Switzerland	61	39	[27-52]	56	[43-69]	49	3.8	[1.0-6.7]
Greece	20	55	[31-79]	50	[26-74]	20	4.6	[2.0-7.5]
Finland	4	75	[0-100]	50	[0-100]	4	3.7	[1.7-5.0]
Israel	61	41	[28-54]	57	[44-70]	56	1.9	[0.2-6.5]
Netherlands	6	50	[0-100]	50	[0-100]	6	1.9	[0.5-4.7]
Portugal	6	33	[0-88]	83	[40-100]	6	6.1	[0.5-12.3]
Spain	104	40	[31-50]	10	[4-16]	96	6.1	[3.0-7.7]
Belgium	17	53	[26-79]	29	[5-54]	16	5.8	[2.6-8.5]
France	97	55	[45-65]	39	[29-49]	96	3.3	[0.8-6.5]
Subtotal †	**525**	**44**	**[40-48]**	**40**	**[35-44]**	**489**	**5.0**	**[1.2-7.5]**
United-Kingdom	80	43	[31-54]	45	[34-56]	53	3.2	[0.7-5.2]
Italy	128	41	[33-50]	46	[38-55]	127	4.7	[0.7-8.2]
Sweden	46	35	[20-49]	29	[16-43]	43	6.4	[1.5-10.2]
Serbia	16	25	[1-49]	31	[6-57]	16	8.3	[2.3-12.4]
Czech Republic	13	54	[22-85]	45	[10-81]	13	5.1	[3.9-11.2]
Romania	8	75	[36-100]	88	[58-100]	8	1.1	[0.3-8.0]
Turkey	102	46	[36-56]	71	[62-80]	102	7.3	[3.7-10.5]
Germany	57	33	[21-46]	46	[33-60]	38	5.0	[1.4-8.6]
Norway	28	43	[23-62]	32	[14-51]	9	5.2	[3.2-6.9]
Total	**1003**	**43**	**[40-46]**	**44**	**[41-47]**	**897**	**5.3**	**[1.2-8.2]**

* date of diagnosis, sex, or information on *situs inversus* were missing for some patients; † the subtotal summarises results for all countries with a response rate of >60%

CI, confidence interval; IQR, interquartile range

Table 4: Determinants of age at diagnosis of PCD patients aged 0-19 years at time of the survey (n=897)

	N	Unadjusted Geometric mean (years)	p	Adjusted* Geometric mean (years)	p
Sex†					
Male	510	4.56	0.316	4.97	0.581
Female	383	4.83		5.09	
***Situs*†**					
Situs solitus	492	5.84	<0.001	4.97	<0.001
Situs inversus	389	3.50		3.40	
Type of centre					
Tertiary	797	4.68	0.707	-	-
Secondary or primary	100	4.52		-	
Number of PCD patients cared for					
1 to 10	368	4.79	0.002	4.97	<0.001
11 to 20	218	5.34		5.03	
21 and more	311	4.11		3.97	
European region					
Western	232	4.03	0.001	4.97	<0.001
British Isles	53	3.50	0.260	4.75	0.641
Southern	268	5.05	0.002	6.45	<0.001
Northern	107	4.63	0.150	5.51	0.164
Eastern	237	5.26	<0.001	6.80	<0.001

European regions: Western Europe: Austria, Belgium, France, Germany, Netherlands, Switzerland; British Isles: Ireland, United-Kingdom; Southern Europe: Cyprus, Greece, Italy, Portugal, Spain; Northern Europe: Denmark, Finland, Norway, Sweden; Eastern Europe: Bulgaria, Czech Republic, Estonia, Hungary, Israel, Romania, Serbia, Slovakia, Turkey

*Adjusted for sex, current age, *situs inversus*, number of PCD patients cared for and EU region; Age at diagnosis at baseline (male, *situs solitus*, 1 to 10 PCD patients cared for, average current age (10.4 years), Western Europe) **= 4.97 years**

† Sex or *situs* were missing for some patients

FIGURE LEGENDS

Figure 1: Age distribution at time of the survey of all reported PCD patients (n=1187)

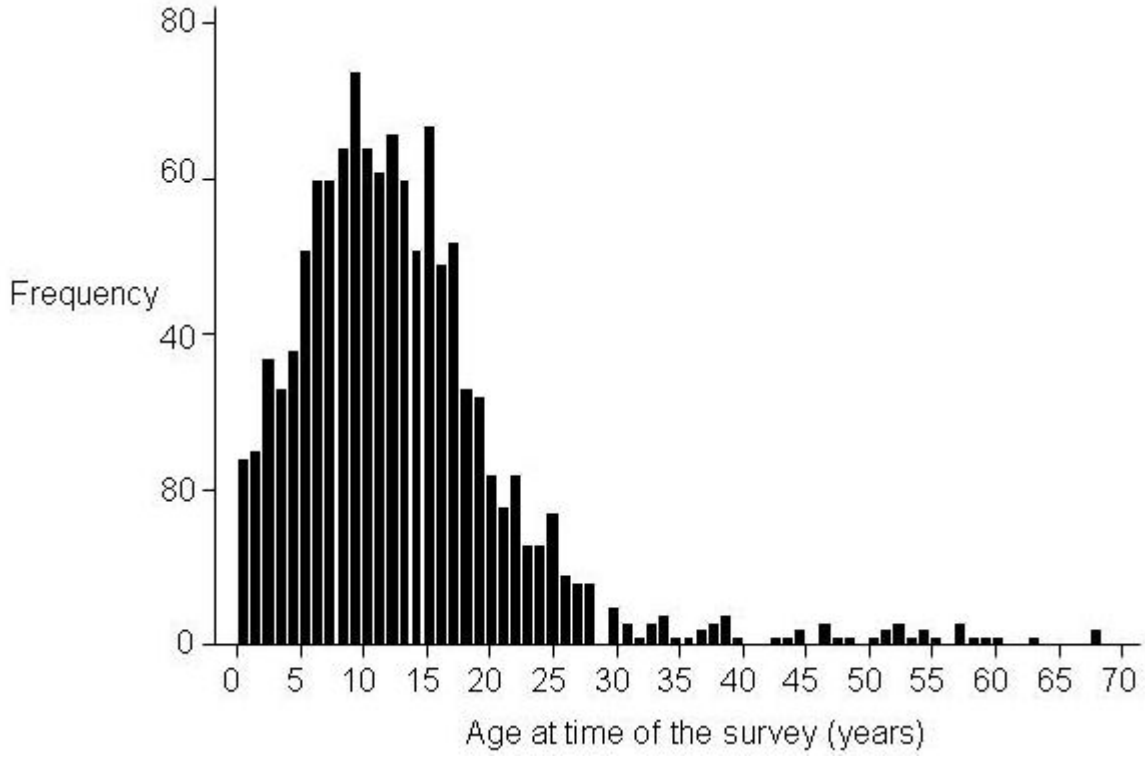
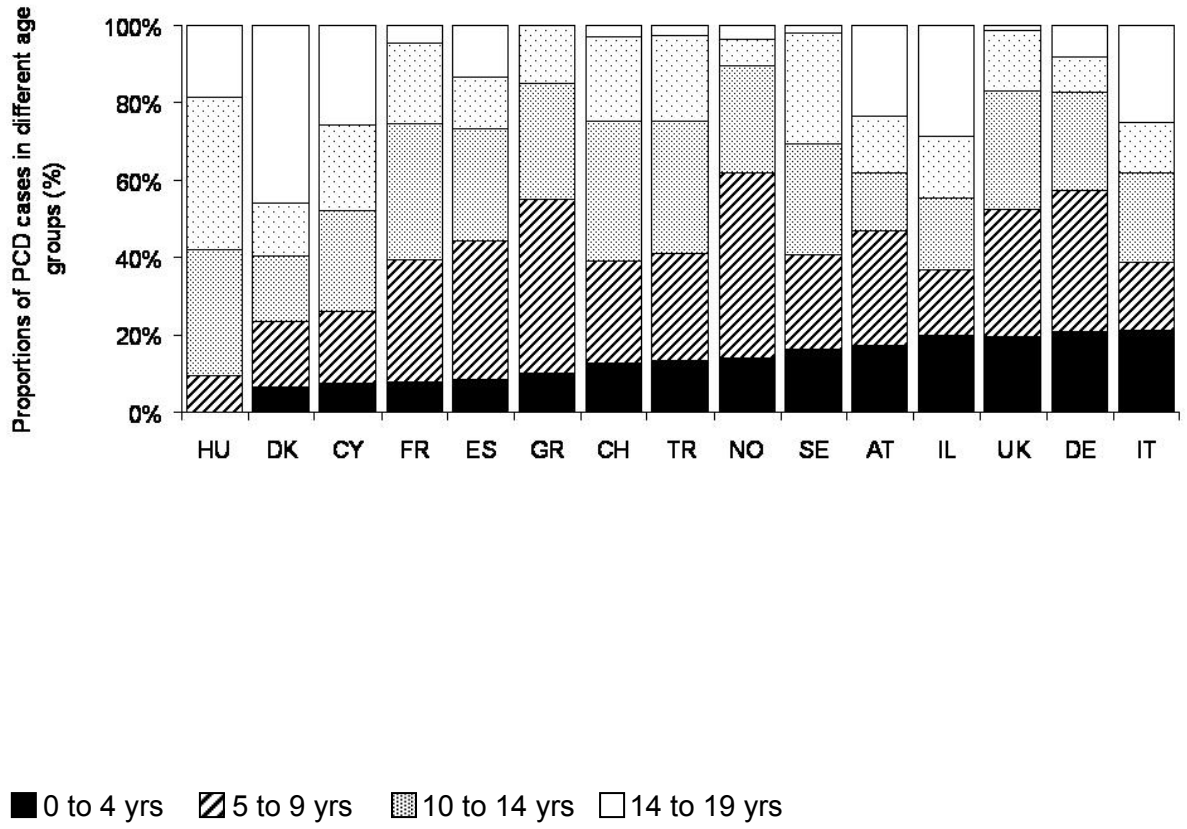


Figure 2: Proportions of PCD patients in different age groups, by country (countries with more than 20 reported PCD patients)



AT: Austria; CH; Switzerland; CY: Cyprus; DE: Germany; DK: Denmark; ES: Spain; FR: France; GR: Greece; HU: Hungary; IL: Israel; IT: Italy; NO: Norway; SE: Sweden; TR: Turkey; UK: United-Kingdom

Figure 3: Reported number of children with PCD aged 5-14 years at time of the survey, per million inhabitants aged 5-14 years, by country

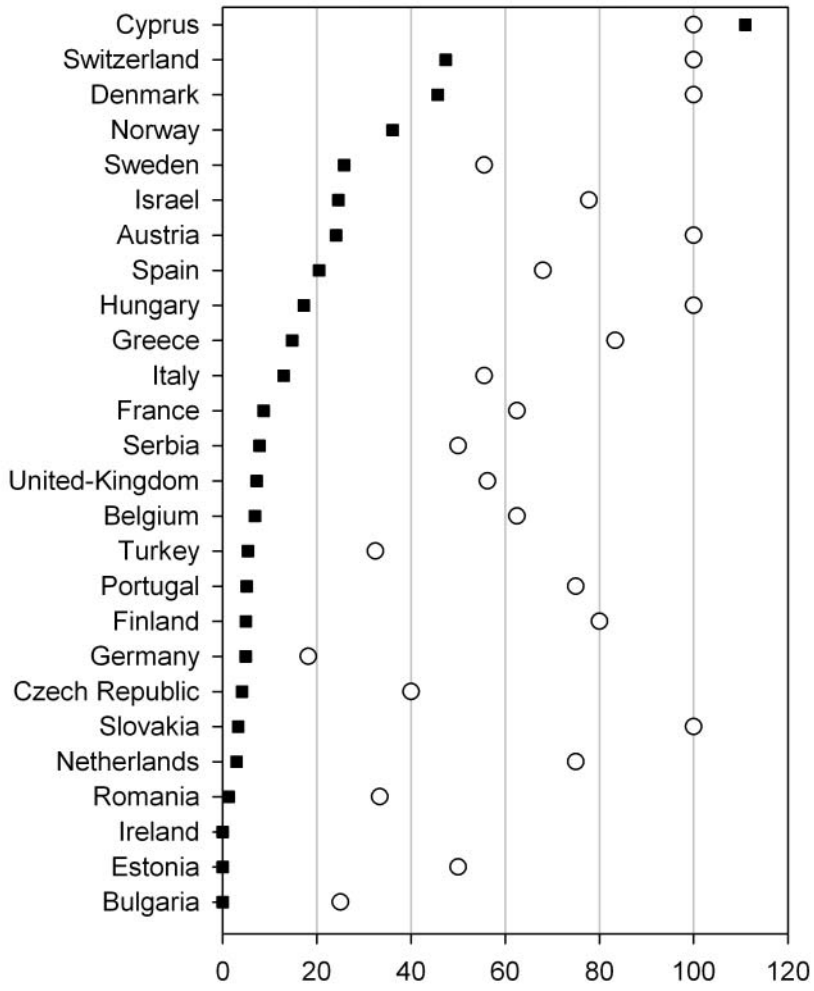
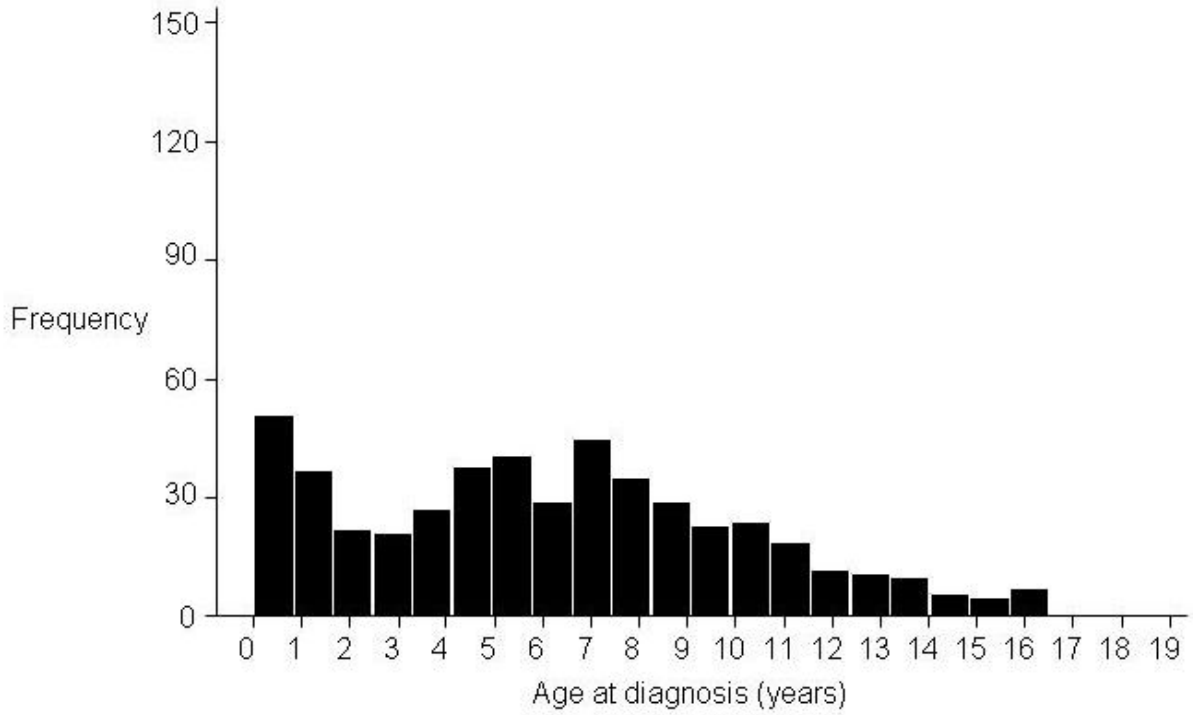


Figure 4: Distribution of age at diagnosis of PCD patients aged 0-19 years at time of the survey, by *situs solitus* / *situs inversus* (n=897)

a) Situs solitus



b) Situs inversus

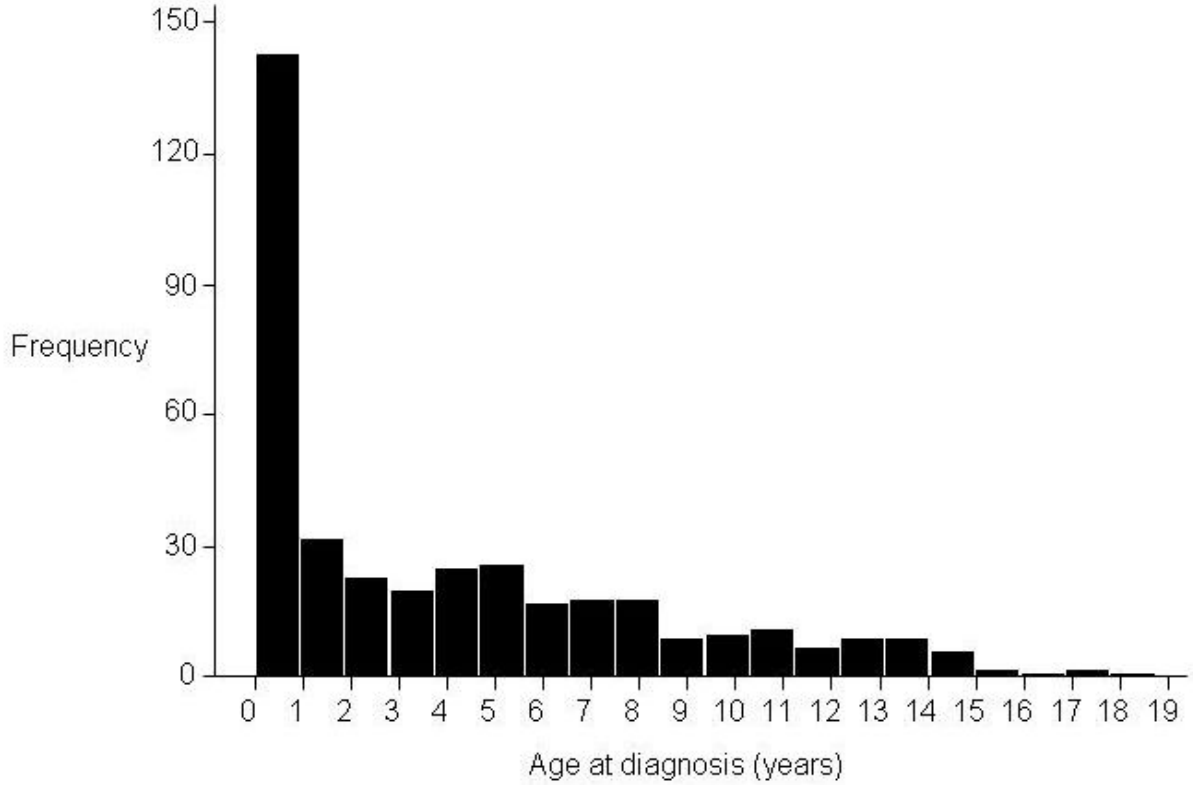
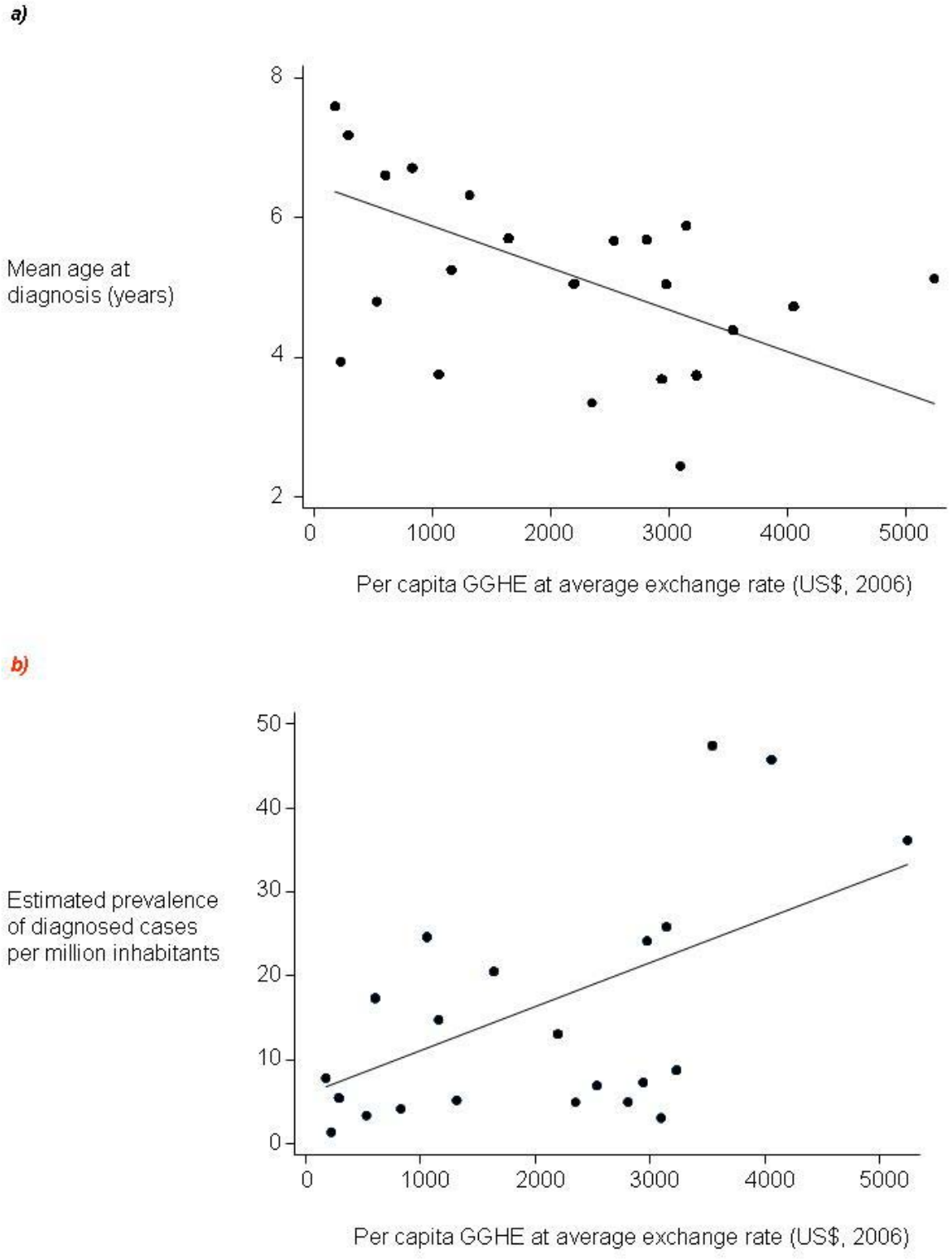


Figure 5: Association between the general government expenditure on health (GGHE) in the country and a) mean age at diagnosis of PCD patients aged 0-19 years at time of the survey and b) prevalence of diagnosed patients per million inhabitants aged 5-14 years (excluding Cyprus, n=25)



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CONFLICT OF INTEREST

None

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