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Social, Educational, and Vocational Outcomes in Patients with Childhood Onset and Young Adult Onset Growth Hormone Deficiency

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Abbreviated title: Outcomes of Onset of GHD before the age of 25

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Abstract

Objective: Hypopituitarism diagnosed in childhood, adolescence and young adulthood has the potential to affect growth and somatic development. Less is known about the impact of such a diagnosis on other aspects of development.

Design: An analysis of the KIMS Database (Pfizer International Metabolic Database) was performed to explore social, educational and vocational outcomes of adult patients diagnosed in childhood, adolescence and young adulthood compared with adult-onset controls.

Patients: 2952 adult patients diagnosed with hypothalamic pituitary conditions before the age of 25 were divided into 2 groups: childhood-onset [<16 years (CO)] ($n=1782$) and young-adult-onset [$16- <25$ years (YAO)] ($n=1170$). 1617 adult patients diagnosed with a non-functioning pituitary adenoma at the age of 25 or older formed the adult-onset control group (AO).

Measurements: KIMS Patient Life Situation Form which provided information on: social, educational and vocational outcomes.

Results: Compared with the AO control group CO and YAO patients were between 4.5 and 8.0 times more likely to live with their parents in adulthood, CO and YAO patients were also less likely to live in partnership and to have children. The impact on educational and vocational outcomes was less marked than on social outcomes with no significant differences compared with the AO control group. Educational and vocational outcomes showed the lowest level in male and female CO and YAO patients who had been previously diagnosed with a brain tumour.

Conclusions: Social outcomes were more affected than educational and vocational outcomes. Although CO patients are more adversely affected, YAO patients were also failing to achieve social milestones. This has consequences for the delivery of endocrine care in both paediatric and adult services.

Introduction

1. Growing up with hypopituitarism through adolescence and young adulthood has the potential to affect physical, psychological and social development as well as interrupting educational and vocational trajectories of the young person. Physical development has been well studied, focussing on outcomes of adult height ¹ and somatic development ², which are known to be affected by hypopituitarism and in particular growth hormone deficiency (GHD). Less is known about the achievement of the five milestones associated with entering adulthood including completing school/education, beginning one's professional career, leaving home, building a stable relationship and becoming a parent. Achieving these

milestones is of significant importance to the development of an adult identity, quality of life, emotional adjustment and functioning in society.

2. A recent study examining social, educational and vocational outcomes in young people with long term conditions identified 4 distinct patterns, 1) those that developed normally, 2) those that achieved educational and vocational goals but underperformed socially, 3) those that despite poor achievement in education and vocation were able to succeed socially and 4) slow developers who underperformed in education, vocation and social arenas³.
3. Previous studies have focused on hypothalamic pituitary conditions with GHD of childhood-onset (CO)⁴⁻¹² but have not examined the impact of being diagnosed in late adolescence and young adulthood, a key time for focusing on education and vocation and also for social change. The aim of this study is therefore to explore the social, educational and vocational outcomes of patients with hypothalamic-pituitary conditions with GHD diagnosed in childhood (<16 years) and late adolescence and young adulthood (16-<25 years).

Subjects & Methods

Subjects

1. This was a retrospective analysis of data from hypopituitary adults with GH deficiency (GHD) obtained from KIMS (Pfizer International Metabolic Database) who were enrolled between 1994 and October 2011. 15 725 patients from 31 countries were included in the database at the cut-off point. The KIMS database was searched to identify patients who had been diagnosed with a hypothalamic pituitary conditions or a condition that results in hypothalamic pituitary dysfunction before the age of 25 and who had completed the KIMS Patient Life Situation Form (KIMS PLSF). The KIMS Database was approved by the Institutional Review Boards, as required by local regulations in each participating country. All patients were informed about the KIMS study and consent was gained in written form for their participation. KIMS is conducted according to the Declaration of Helsinki¹³.
2. Patients were divided into 2 groups by age of diagnosis: CO <16 years and Young-Adult-Onset (YAO) 16-<25 years. In the CO and YAO groups patients were included if they had a non-acquired diagnosis including congenital and idiopathic causes (NA) or a diagnosis of a craniopharyngioma (CP), pituitary adenoma (PA), brain tumour (BT) or haematological malignancy (HM). The AO control group was age matched rather than condition matched and included adult-onset (AO) patients diagnosed with a non-functioning pituitary adenoma (NFPA) at the age of 25 or older who had completed the KIMS PLSF formed. This control group was chosen as they represent the largest group of AO patients included on the KIMS database thereby reducing heterogeneity of differing diagnoses with identical data collection.

KIMS Patient Life Situation Form

3. The KIMS PLSF is a patient-reported outcome questionnaire translated into the native language of participating countries and back translated into English to ensure accuracy of meaning. The questionnaire is given to the patient in clinic for self-completion, asking questions about personal and social situations including education and vocation¹⁴. Types of employment are described as professional and/or non-manual salaried employee to mean

professional, managerial or administrative as opposed to blue collar which means manual labour.

Statistical Analysis

4. Data from individual patients were analysed in 3 age bands (25-35, 35-45, 45-55 years), using data closest to the middle of each age band (a patient can be represented in more than one age band but only once in each age band). Percentages of patients achieving each outcome were calculated. CO and YAO patients were compared as a whole group and by diagnostic category with the AO control group using Fisher Exact Test. Different diagnostic groups were compared using least mean squares. Taking the percentage of the equivalent AO control group as equalling 1, fold differences were calculated for the 35-45 age band only. This age band was chosen due to the largest numbers across CO (n=523), YAO (n=411) and AO (n=495) groups and also represents an age at least 10 years or longer after diagnosis for CO and YAO patients and by which most outcomes are anticipated to have been completed.
5. Forward stepwise linear regression was performed on the last available KIMS PLSF in each patient in the CO and YAO groups to identify factors influencing each outcome. Variables included current age, gender, diagnosis, age and calendar year at diagnosis of the hypothalamic pituitary condition or the condition that results in hypothalamic pituitary dysfunction, treatment factors (radiotherapy (XRT) and surgery), number of additional pituitary hormone deficiencies and adult height SDS. Age and gender corrected height expressed as a Standard Deviation Score (SDS) from the mean height of a normal population was calculated. SDS: 0=Normal height, -2SDS=Shorter than 2.5% of the population, +2SDS=Taller than 97.5% of the population.
6. Statistical procedures were conducted using the Statistical Analysis System (SAS Institute, Inc, Cary, NC). Statistical significance was taken as $p < 0.05$ (Fisher Exact Test and forward stepwise regression) and $p < 0.01$ (Least Mean Squares) due to multiple comparisons.

Results

1. 2952 patients diagnosed before the age of 25 were identified in the KIMS database; 1782 childhood-onset [<16 years (CO)] and 1170 young-adult-onset [$16- <25$ years (YAO)] patients. The control group comprises of 1617 AO NFPA patients. The patients come from 27 countries with the largest contribution from UK (n=1071) followed by Germany (n=994) and Sweden (n=688). Belgium, the Netherlands, Spain, France, Czech Republic and Denmark all contributed more than 100 patients.
2. CO and YAO patients and AO control group characteristics are presented in Table 1 by diagnosis & Table 2 in the 35 to 45 age band.

SOCIAL OUTCOMES - LIVING WITH PARENTS & LIVING IN PARTNERSHIP AND HAVING CHILDREN
3. In the group as a whole regardless of age band and diagnostic group in adulthood CO and YAO patients were more likely to live with their parents than AO NFPA controls. At the age of 35 to 45 CO and YAO patients were four times more likely to live with their parents, while CO females were eight times more likely to live with their parents in adulthood (Table 3).

Some differences were seen between diagnostic groups: CO females with craniopharyngiomas were more likely to live with their parents compared with those with pituitary adenomas and non acquired diagnoses; YAO males with brain tumours were more likely to live with their parents compared with those with pituitary adenomas (Figure 1).

4. In the group as a whole regardless of age band and diagnostic group CO and YAO patients were less likely to live in partnership and have children than AO NFPA controls. At the age of 35 to 45 around half the number of CO patients expected, based on levels observed in AO controls, lived in partnership and only a third to a quarter had children, and around two thirds to three quarters the number of YAO patients expected lived in partnership and over half had children (Table 3). The only difference observed between diagnostic groups was in CO females with brain tumours who were less likely to have children than CO females with a non acquired diagnosis.
5. The results of forward stepwise regression adjusted for age showed that in the combined CO and YAO groups, patients with fewer pituitary hormone deficiencies and of taller stature were less likely to live with their parent while patients with the diagnosis of a pituitary adenoma were more likely to live in partnership and have children. Female patients were less likely to live with their parents and more likely to live in partnership. A diagnosis of a brain tumour was associated with living with their parents, and not having undergone radiotherapy was associated with living in partnership. A later calendar year at diagnosis was associated with improved social outcomes (Table 4).

EDUCATIONAL AND VOCATIONAL OUTCOMES - HIGHER EDUCATION & BEING IN EDUCATION, EMPLOYMENT OR TRAINING (EET)

6. In the whole group no differences were found for completing higher education or being in EET compared with AO NFPA controls (Table 3). Females with brain tumours had lower levels of being in EET than AO controls. CO female brain tumour patients had significantly lower levels of being in EET than CO patients with non acquired diagnoses or craniopharyngiomas (Figure 2).
7. Analysis by forward stepwise regression identified that being of taller stature, a fewer number of pituitary hormone deficiencies, and a later year at diagnosis were associated with having received higher education. Being in EET was associated with a later year at diagnosis and not having the diagnosis of a brain tumour, being male and not having radiotherapy (Table 4). The factors associated with being in full time employment rather than part time were being male, not having a brain tumour, having a pituitary adenoma and not having had radiotherapy. Those in white collar work rather than blue collar work were older age at diagnosis, were more often females, having had radiotherapy and not having a brain tumour (Table 4).

Discussion

1. Patients diagnosed with hypothalamic pituitary conditions before the age of 25 are failing to successfully achieve the social outcomes of adult life. Although CO patients are more markedly affected, YAO patients also have significantly decreased social outcomes even at the ages of 35 to 45 years across a range of diagnoses. ~~This remains true for YAO patients diagnosed with pituitary adenomas, potentially the group with a closer match to the control group of AO patients with NFPA, suggesting it is the age of onset rather than the disease process that is implicated in reduced outcomes.~~ Educational and vocational outcomes are

less affected in comparison.

2. This study confirms the finding of other studies that CO patients with hypopituitarism are adversely affected in respect to achieving their social outcomes^{4, 7-10}. A meta-analysis of studies examining similar outcomes in 25 year old patients with different CO long term conditions compared with healthy peers found a similar level for living in partnership, but higher levels of leaving home compared with this current study (22% living with parents compared with 33-37% in this study) and in having children (38% having children compared with 9% in this study)¹⁵. This suggests that CO patients with hypopituitarism with GHD are among the long term conditions most adversely affected with regards to social outcomes. The current study now demonstrates that YAO patients diagnosed with hypopituitarism have also not avoided the social consequences. This is despite a shorter duration of disease, potentially starting at a time when social trajectories had already been set.
3. The reasons for patients with hypopituitarism failing to achieve social outcomes are likely to be multifactorial and similar to those faced by others growing up with a long term condition. In this study fewer CO and YAO patients had visual field defects and a higher percentage had epilepsy than AO controls, and while levels of requiring assistance with ADLs was similar higher percentages of CO and YAO patients required assistance with dressing and personal hygiene indicating reduced levels of independence. The number of pituitary hormone deficits and adult height was an associated factor across social as well as educational and vocational outcomes, in particular, in living with parents and not having higher education. Previous studies have identified an association with degree of hypopituitarism and psychosocial outcome⁸. The effect of height has been extensively studied with short stature in either health or illness being predominantly reported in males with poorer outcomes throughout the lifespan^{5, 7, 12}. These data reflect the health burden of the condition and also the visibility. This will potentially influence the real or perceived need for ongoing involvement of parents¹⁴, limit opportunities to participate in educational and social activities¹⁵, alter an individual's own life goals¹⁶ and may expose them to discrimination¹⁷, all of which have been associated with achieving lower levels of independence. ~~Patients with hypopituitarism may experience difficulties in self-confidence and the ability to socialise with their peer group, which can all hinder the chances of living independently, living with a partner and having children. In a range of long term conditions limitations in functional ability and participation in social activities, as well as absenteeism from school, university/college, or workplace may negatively affect the achievement of these milestones¹⁵. Lesser academic achievement, lower employment, and delayed independence may also result from an alteration in an individual's life goals, for example, when having to invest a lot of time in illness management¹⁶. In addition, negative attitudes toward individuals with chronic illness or disabilities may contribute to their lower success in mastering tasks associated with adult life¹⁷. There is evidence of discrimination against individuals with chronic illness and disability when applying for a job and in the workplace in general^{18, 19}. In addition, parents of young people with chronic physical illness are, on average, more overprotective than other parents¹⁴. This may inhibit the development of an independent life in adulthood. There is retrospective evidence that intervention to enhance life skills empowers young people and provides parental hope¹⁸ and prospective studies are ongoing¹⁹.~~

3b.

Reduced fertility due to gonadotrophin deficiency and/or ovarian damage secondary to chemotherapy and/or radiotherapy is likely to have influenced the low numbers having children. Due to 80% of CO and YAO patients being recorded as having gonadotrophin

deficiency it was not possible to evaluate whether those with intact gonadal axes had a higher rate of having children. Further research is required as to whether options for fertility are adequately discussed and offered to patients.

4. This current study found minimal differences in level of education and also employment, with differences being confined to certain diagnostic groups or being specific to gender, for example, females with brain tumours had lower levels of being in education, employment and training (EET). A study from Denmark identified a lower education level, lower income and higher risk of retirement¹¹ and the meta-analysis across a range of long term conditions identified a 25% reduction in employment¹⁵. This lack of difference is potentially explained by our control group having been born earlier when opportunities for training and employment may have been lower and also having a long term condition which is known to have reduced employment. More detailed analysis such as income may have yielded differences as in previous studies. The group that was adversely affected were those with brain tumours regardless of age of onset and particularly females, who were less likely to be in EET. This has been previously shown and is likely to be due in part to the neurocognitive sequelae as a direct consequence of having a brain tumour and intensity of cancer treatment including radiotherapy²⁰⁻²².
5. The later year (rather than age) of diagnosis, that is, being diagnosed more recently had a positive impact on all outcomes but particularly EET which may reflect improved medical care and/or support provided in education. This was also identified in the meta-analysis, later publications had less reduction in income compared with healthy peers¹⁵.
6. When interpreting this data, it is important to recognise that patients in the KIMS database potentially represent the more severely affected patients with hypopituitarism and GHD and reduced quality of life. The control group, AO patients with NFPA, identified from the same database, also have a long term condition, and therefore if patients had been compared with healthy peers the deficits would potentially have been greater. The advantages of this approach include similarities in data collection using the same tool and the fact that the control group is representative of patients attending the same clinics as the CO and YAO patients. The disadvantages are that the control group was not matched for year of birth and on average were born 10-15 years earlier than the CO and YAO cohort, resulting in different trends regarding living with parents, education, employment and training. In addition it is not possible with this retrospective analysis to comment on causation but simply association of possible contributing factors.
7. In summary, children, adolescents and young adults diagnosed with hypopituitarism persistent into adulthood are failing to achieve their social outcomes. Although social, educational and vocational outcomes are both recognised as important determinants of long term health, there is more of a focus on making young people employable and economically active than helping with social skills and opportunity for peer interaction. This is despite social relationships being shown to be particularly important in increasing resilience and promoting recovery. A previous study in CO patients with GHD demonstrated a reduction in likelihood of death once socioeconomic factors were adjusted for¹¹. Future research should focus on the benefit of programmes to support increasing independence and peer interaction to reduce the barriers to adjusting to adult life.

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References

- 1 Pfaffle, R. (2015) Hormone replacement therapy in children: The use of growth hormone and IGF-I. *Best Pract Res Clin Endocrinol Metab* **29**, 339-352.
- 2 Hogler, W. & Shaw, N. (2010) Childhood growth hormone deficiency, bone density, structures and fractures: scrutinizing the evidence. *Clin Endocrinol (Oxf)* **72**, 281-289.
- 3 Sattoe, J.N., Hilberink, S.R., van Staa, A. & Bal, R. (2014) Lagging behind or not? Four distinctive social participation patterns among young adults with chronic conditions. *J Adolesc Health* **54**, 397-403.
- 4 Dean, H.J., McTaggart, T.L., Fish, D.G. & Friesen, H.G. (1985) The educational, vocational, and marital status of growth hormone-deficient adults treated with growth hormone during childhood. *Am J Dis Child* **139**, 1105-1110.
- 5 Kao, K.T., Stargatt, R. & Zacharin, M. (2015) Adult Quality of Life and Psychosocial Outcomes of Childhood Onset Hypopituitarism. *Horm Res Paediatr* **84**, 94-101.
- 6 Keselman, A., Martinez, A., Pantano, L., Bergada, C. & Heinrich, J.J. (2000) Psychosocial outcome in growth hormone deficient patients diagnosed during childhood. *J Pediatr Endocrinol Metab* **13**, 409-416.
- 7 Lagrou, K., Xhrouet-Heinrichs, D., Massa, G., Vandeweghe, M., Bourguignon, J.P., De Schepper, J., de Zegher, F., Ernould, C., Heinrichs, C., Malvaux, P. & Craen, M. (2001) Quality of life and retrospective perception of the effect of growth hormone treatment in adult patients with childhood growth hormone deficiency. *J Pediatr Endocrinol Metab* **14 Suppl 5**, 1249-1260; discussion 1261-1242.
- 8 Rikken, B., van Busschbach, J., le Cessie, S., Manten, W., Spermon, T., Grobbee, R. & Wit, J.M. (1995) Impaired social status of growth hormone deficient adults as compared to controls with short or normal stature. Dutch Growth Hormone Working Group. *Clin Endocrinol (Oxf)* **43**, 205-211.
- 9 Sandberg, D.E. & MacGillivray, M.H. (2000) Growth hormone therapy in childhood-onset growth hormone deficiency: adult anthropometric and psychological outcomes. *Endocrine* **12**, 173-182.
- 10 Sandberg, D.E., MacGillivray, M.H., Clopper, R.R., Fung, C., LeRoux, L. & Alliger, D.E. (1998) Quality of life among formerly treated childhood-onset growth hormone-deficient adults: a comparison with unaffected siblings. *J Clin Endocrinol Metab* **83**, 1134-1142.
- 11 Stochholm, K., Juul, S., Christiansen, J.S. & Gravholt, C.H. (2012) Mortality and socioeconomic status in adults with childhood onset GH deficiency (GHD) is highly dependent on the primary cause of GHD. *Eur J Endocrinol* **167**, 663-670.
- 12 Takano, K., Tanaka, T. & Saito, T. (1994) Psychosocial adjustment in a large cohort of adults with growth hormone deficiency treated with growth hormone in childhood: summary of a questionnaire survey. Committee for the Study Group of Adult GH Deficiency. *Acta Paediatr Suppl* **399**, 16-19; discussion 20.
- 13 Riis, P. (2003) Thirty years of bioethics: the Helsinki Declaration 1964-2003. *New Rev Bioeth* **1**, 15-25.
- 14 Saller, B., Mattsson, A.F., Kann, P.H., Koppeschaar, H.P., Svensson, J., Pompen, M., Koltowska-Haggstrom, M., German, K.i., Dutch, K.i. & Swedish, K.i. (2006) Healthcare utilization, quality of life and patient-reported outcomes during two years of GH replacement therapy in GH-deficient adults--comparison between Sweden, The Netherlands and Germany. *Eur J Endocrinol* **154**, 843-850.
- 15 Pinquart, M. (2014) Achievement of developmental milestones in emerging and young adults with and without pediatric chronic illness--a meta-analysis. *J Pediatr Psychol* **39**, 577-587.
- 16 Maslow, G.R., Haydon, A., McRee, A.L., Ford, C.A. & Halpern, C.T. (2011) Growing up with a

chronic illness: social success, educational/vocational distress. *J Adolesc Health* **49**, 206-212.

17 Gledhill, J., Rangel, L. & Garralda, E. (2000) Surviving chronic physical illness: psychosocial outcome in adult life. *Arch Dis Child* **83**, 104-110.

18 McPherson, A., Rudzik, A., Kingsnorth, S., King, G., Gorter, J. & Morrison, A. (2016) "Ready to take on the world": Experiences and understandings of independence after attending residential immersive life skills programs for youth with physical disabilities. *Dev Neurorehabil* **22**, 1-10.

19 McPherson, A., King, G., Rudzik, A., Kingsnorth, S., Gorter, J. & OIPR (2016) Optimizing life success through residential immersive life skills programs for youth with disabilities: study protocol of a mixed-methods, prospective, comparative cohort study. *BMC Pediatr* **16**(1), 153.

20 Gunn, M.E., Mort, S., Arola, M., Taskinen, M., Riikonen, P., Mottonen, M. & Lahteenmaki, P.M. (2015) Quality of life and late-effects among childhood brain tumor survivors: a mixed method analysis. *Psychooncology*.

21 Woodgate, R.L., Tailor, K., Yanofsky, R. & Vanan, M.I. (2016) Childhood brain cancer and its psychosocial impact on survivors and their parents: A qualitative thematic synthesis. *Eur J Oncol Nurs* **20**, 140-149.

22 Zebrack, B.J., Gurney, J.G., Oeffinger, K., Whitton, J., Packer, R.J., Mertens, A., Turk, N., Castleberry, R., Dreyer, Z., Robison, L.L. & Zeltzer, L.K. (2004) Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol* **22**, 999-1006.

TABLE 1

CO AND YAO PATIENTS DIVIDED BY DIAGNOSIS AND AO CONTROL GROUP CHARACTERISTICS

	Non acquired		Craniopharyngioma		Pituitary adenoma		Brain tumour		Haematological Malignancy		NFPA
	CO	YAO	CO	YAO	CO	YAO	CO	YAO	CO	YAO	AO
All (number)	777	83	442	229	129	675	381	173	53	10	1617
Male (number)	462	49	230	127	73	270	180	72	22	3	891
Mean age of diagnosis (years)	8.2	20.3	10.4	20.1	12.7	21.0	10.0	20.6	9.3	21.4	39.1
Mean age at last PLS (years)	35.0	38.4	36.2	37.8	36.3	39.8	32.3	35.6	31.0	30.4	47.9
Mean year of diagnosis	1978	1984	1979	1986	1981	1985	1983	1990	1985	1998	1995
Number of additional pituitary hormone deficiencies	1.9	2.2	3.5	3.2	2.6	2.4	2.1	2.3	0.8	0.5	2.4
Adult Ht SDS	-1.6	-1.9	-0.7	-0.5	-0.8	-0.2	-1.4	-0.4	-1.4	-0.9	+0.1

TABLE 2

PERCENTAGE OF CO AND YAO PATIENTS AND AO CONTROL GROUP IN THE 35 TO 45 AGE GROUP WITH INDIVIDUAL PITUITARY DEFICIENCIES, PHYSICAL DISABILITIES AND REQUIRE ASSISTANCE WITH ACTIVITIES OF DAILY LIVING

	% who had XRT	% with Individual Pituitary Hormone Deficiencies				% with Physical Disability			% requiring assistance with Activities of Daily Living				
		ACT H	LH/FSH	TSH	DI	VFD	Ophthalmoplegia	Epilepsy	ADLS	Shopping	Housekeeping	Grooming Dressing	Personal Hygiene
CO	29.2	63.3	79.6	78.8	30.8	40.9	10.2	7.5	15.5	7.5	10.7	2.4	2.6
YAO	52.8	74.0	83.2	74.2	30.1	42.9	8.6	6.8	16.8	10.1	12.7	1.8	1.8
AO controls	34.7	66.9	73.6	66.2	22.3	60.3	10.4	1.5	16.2	7.5	10.6	0.4	0.2
	P<0.01	P<0.01	P<0.01	P<0.01	P<0.01	P<0.01	ns	P<0.01	ns	ns	ns	P=0.03	P<0.01

TABLE 3

SOCIAL, EDUCATIONAL AND VOCATIONAL OUTCOMES IN CO AND YAO PATIENTS BY AGE BAND INCLUDING AO CONTROL GROUP

Number of patients/ Number of observations (%)	Living with Parents			Living in partnership			Having children			Having higher education			Being in Education, Employment or Training		
Males	CO	YAO	AO	CO	YAO	AO	CO	YAO	AO	CO	YAO	AO	CO	YAO	AO
25-35 years	204/54637†	83/22138†	5/4411	138/54925*	65/22529*	23/4551	49/5609*	32/22914*	15/4533	200/54437	104/22138	17/4538	439/54281	172/21779	37/4484
35-45 years	65/27823†	41/16225†	13/2455	112/28439*	87/16652*	188/24876	58/29020*	71/16942*	182/25073	90/28032	57/16335	97/24440	224/27980	128/16180	193/24479
45-55 years	20/11517†	18/12015†	12/6042	53/11646*	62/12350*	493/60581	32/11727*	48/12339*	522/61884	40/11435	40/12233	208/5935	82/11373	96/12279	439/59674
35-45 years Fold difference	4.6	5.0	1	0.51	0.68	1	0.27	0.58	1	0.80	0.83	1	1.01	1.01	1
Females															
25-35 years	156/47233†	46/24719†	3/565	154/48532*	128/25450*	39/5670	45/4899*	70/25827*	30/5753	220/47946	106/24843	22/5739	349/47074	197/24780	44/5481
35-45 years	35/22416†	21/2319†	5/2362	100/22944*	144/23861*	194/23981	57/23324*	112/24246*	183/24575	82/22636	95/23640	83/23635	174/22577	176/2375	192/23283
45-55 years	15/9116†	11/1468†	6/3892	39/9143*	96/14964*	306/39977	22/9324*	78/14952*	334/40283	24/8927	51/14635	114/39129	54/9060*	102/14172	284/38873
35-45 years Fold difference	8.0	4.5	1	0.54	0.75	1	0.32	0.61	1	1.03	1.14	1	0.93	0.90	1

†higher % and * lower % compared with AO controls p<0.05

Proportion calculated by dividing percentage by AO controls in 35-45 year old age band only

TABLE 4

SUMMARY OF FORWARD STEPWISE LINEAR REGRESSION FOR SOCIAL AND EDUCATIONAL AND VOCATIONAL OUTCOMES IN CO AND YAO PATIENTS

Outcomes: Living with parents, living in partnership, had children, higher education, in education, employment or training (EET), in employment, in full time employment, in Professional and/or non-manual salaried employment

Variables: current age, gender (M/F), diagnosis, year and age of diagnosis, treatment factors (XRT & surgery), adult height SDS and number of additional pituitary hormone deficiencies

	Living with parents	Living in partnership	Had children	Higher education	EET	Employment	Full Time	Professional and/or non-manual salaried employee
N	2815	2858	2878	2809	2771	2771	1684	1629
1	Current age (-)	Current age (+)	Current age (+)	Adult height SDS (+)	Year of Diagnoses (+)	Current age (+)	Gender (M+)	Age of onset (+)
2	Number of additional PHD (+)	Pituitary adenoma (+)	Pituitary adenoma (+)	Number of additional PHD (-)	Brain Tumour (-)	Therapy (XRT-)	Brain Tumour (-)	Gender (F+)
3	Adult height SDS (-)	Number of additional PHD (-)	Number of additional PHD (-)	Year of diagnosis (+)	Number of additional PHD (-)	Number of additional PHD (-)	Pituitary adenoma (+)	Therapy (XRT+)
4	Gender (M+)	Gender (F+)	Year of diagnosis (+)		Gender (M+)	Brain Tumour (-)	Therapy (XRT-)	Brain Tumour (-)
5	Haematological malignancy (-)	Adult height SDS (+)	Adult height SDS (+)		Adult height SDS (+)	Year of Diagnosis (+)		
6	Brain tumour (+)	Therapy (XRT-)			Therapy (XRT-)	Gender (M+)		
7	Year of diagnosis (-)	Year of diagnosis (+)			Age of onset (-)	Age of onset (-)		
8	Age of onset (+)							

1 indicates most significant factor

+/- indicates whether the association is positive or negative

Figure Legends

Figure 1 : Fold Difference (y axis) of CO and YAO Males and Females with Different Diagnoses for Social outcomes from AO NFPA Controls (=1)

Brain tumour (BT), Craniopharyngioma (CP), Non acquired diagnoses (NA), Pituitary adenoma (PA) (Haematological malignancy data not shown due to small numbers),

P<0.05 *compared with NFPA Controls regardless of diagnosis

P<0.05 ** individual diagnoses compared with NFPA Controls

P<0.01 †^{1vs 2 etc} individual diagnoses compared BT¹, CP², NA⁴ and PA⁵

Figure 2 : Fold Difference (y axis) of CO and YAO Males and Females with Different Diagnoses for Educational and Vocational outcomes from AO NFPA Controls (=1)

Brain tumour (BT), Craniopharyngioma (CP), Non acquired diagnoses (NA), Pituitary adenoma (PA) (Haematological malignancy data not shown due to small numbers),

P<0.05 *compared with NFPA Controls regardless of diagnosis

P<0.05 ** individual diagnoses compared with NFPA Controls

P<0.01 †^{1vs 2 etc} individual diagnoses compared BT¹, CP², NA⁴ and PA⁵

Figure 1: Fold Difference (y axis) of CO and YAO Males and Females with Different Diagnoses for Social outcomes from AO NFPA Controls (=1)

Figure 2: Fold Difference (y axis) of CO and YAO Males and Females with Different Diagnoses for Educational and Vocational outcomes from AO NFPA Controls (=1)