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ORIGINAL RESEARCH

Trends in Developmental, Behavioral and Somatic Factors by Diagnostic Sub-group in Pervasive Developmental Disorders: A Follow-up Analysis

Paul Whiteley[1], Lynda Todd[1], Kalliopi Dodou[2] and Paul shattock[1]

[1]Department of Pharmacy, Health & Well-being, Faculty of Applied Sciences, University of Sunderland, UK.
[2]Senior Lecturer, Sunderland Pharmacy School, Department of Pharmacy, Health and Well-being, Faculty of Applied Sciences, University of Sunderland, UK.

Dr Whiteley, Ms Todd & Mr Shattock's current address: ESPA Research, The Robert Luff Laboratory, Unit 133i Business & Innovation Centre (BIC), Sunderland Enterprise Park, Wearfield, Sunderland SR5 2TA, UK.
Email: paul.whiteley@espa-research.org.uk

Abstract: Differences in the frequency of several somatic conditions have been tentatively reported between the diagnostic sub-groups of pervasive developmental disorder (PDD). Retrospective cross-sectional analysis of a database was used to test these preliminary findings. A sample of 1189 children diagnosed with autism ($n = 267$), Asperger syndrome ($n = 210$) or autism spectrum disorder (ASD) ($n = 712$) were included for study. Parental reporting of PDD sub-groups provided a number of significant ($P < 0.01$) differentiating developmental and behavioral items concomitant with diagnostic guidelines and anticipated level of functioning per grouping. Significant somatic discriminators previously reported between the sub-groups were corroborated; most notably a reported history of the bacterial skin infection impetigo. The majority of the somatic items identified were specifically related to a diagnosis of Asperger syndrome.

Keywords: pervasive developmental disorder, autism, Asperger syndrome, somatic, questionnaire

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Introduction

Although categorised as pervasive developmental disorders (PDDs), conditions such as autism, Asperger syndrome and PDD-not otherwise specified (also known as autism spectrum disorder, ASD in the UK and Ireland) represent clinically discrete disorders according to current diagnostic guidelines and practices.[1,2] This, despite continuing controversies as to the nosological validity of some diagnoses, the exclusivity and degree of overlap between the various conditions and the lack of formal, genetic and/or biological markers as reliable, objective discriminators from each other and asymptomatic controls.[3]

Diagnosis of all PDD sub-groupings currently resides on the basis of observed behaviors and detailed inspection of early developmental history through retrospective questioning of parents/primary caregivers. The seminal descriptions provided by Kanner[4] and Asperger[5] for autism and Asperger syndrome (AS) respectively, implied that the unusual behavioral manifestations depicted were fundamental to distinguishing patients presenting with these conditions from "normally" developing controls. The focus on the overt behavioral manifestations of the conditions whilst crucial has nevertheless tended to overshadow a number of other, more somatically-based observations made by each author. Kanner, in his original case-series for example, described a number of physiological aspects present in his patient group including the presence and effect of viral and bacterial agents, gait and motor co-ordination issues and early infantile feeding problems. Some of these factors are, at last, becoming the focus of investigations.[6]

Several co-morbid medical and somatic factors, outside of the behavioral and cognitive expressions of the condition, have been linked to PDD. Various conditions have been reported to be more frequently present in people with PDD and their families than would have been expected from control groups and population estimates, including psoriasis,[7] arthritis[8] and other more functional problems associated with bowel habits.[9] The majority of studies examining the potential overlap between PDD and somatic symptoms/conditions have tended to rely on either focusing on one specific PDD sub-grouping or combining results from participants with several different PDD diagnoses.

The frequency of various somatic factors contrasted across the various PDD diagnostic sub-groups has also been described.[10] The dataset used in this study was derived from an electronic database of parental responses to a questionnaire. The main findings suggested that whilst trends in the developmental and behavioral presentation of the various sub-groups matched expected clinical descriptions, there was variation in the reporting of a number of somatic features across the sub-groups. Diagnosis of AS seemed to confer greater susceptibility to items such as increased early infantile feeding problems, and a greater frequency of the bacterial skin disorder impetigo. The current paper details a follow-up investigation based on analyses of the original developmental, behavioral and somatic items used in the previous study, with a larger, independent sample of participants.

Methods

As previously detailed, information on participants diagnosed with PDD are collected via a parent-report questionnaire as part of related studies.[11–14] In the current investigation, cross sectional analysis of parental responses to various questionnaire items, described by Whiteley,[10] pertaining to medical and developmental history and current abilities were analysed for an independent group based on records received between December 2002 and November 2007 ($N = 2995$). A number of additional items were also included as part of the current investigation.

Completed records ($n = 1189$) for participants resident in the UK or Republic of Ireland, aged between 3–11 chronological years and in receipt of a formal diagnosis of autism ($n = 267$), Asperger syndrome ($n = 210$) or autism spectrum disorder (ASD) ($n = 712$) [ICD (international statistical classification of diseases) codes F84.0, F84.5, F84.8] were included for study (Table 1). Criteria for formal diagnoses included: parental indication of child's receipt of a formal PDD diagnosis, indication of a specific categorical PDD diagnosis (autism, Asperger syndrome, ASD), recorded date of diagnosis (month/year), details of diagnosing clinician and place where diagnosis was given. Parents were also encouraged where possible to provide copies of the feedback provided during diagnostic assessment detailing the type of instrument used during assessment and any observations

Table 1. Numbers of cases and demographics by PDD diagnostic sub-groups (parentheses for *total cases* show percentages as a function of the total number of cases included in analysis, n = 1189; all other parentheses show percentages according to sub-group totals). Maternal and paternal occupations show the most popular occupations according to SOC2000 codings.

	Autism	AS	ASD
***Total cases**	267 (22)	210 (18)	712 (60)
*Males	230 (86)	193 (92)	625 (88)
*Females	37 (14)	17 (8)	87 (12)
***Mean age (years)**[a]	5.53	7.04	4.85
*SD	2.38	2.22	1.89
Area of residence			
Urban	70 (26)	34 (16)	143 (20)
Suburban	117 (44)	109 (52)	342 (48)
Rural	58 (21)	59 (28)	160 (23)
Missing responses	21 (8)	8 (4)	65 (9)
Maternal ethnicity			
White British	208 (78)	183 (87)	535 (75)
White Irish	24 (9)	12 (6)	65 (9)
Other White	14 (5)	12 (6)	32 (4)
Other background	21 (8)	3 (1)	79 (11)
Paternal ethnicity			
White British	204 (76)	189 (90)	537 (75)
White Irish	25 (9)	10 (5)	63 (9)
Other White	11 (4)	6 (3)	27 (4)
Other background	20 (7)	5 (2)	85 (12)
Missing responses	1 (–)	–	–
Current maternal occupation			
At home	121 (45)	74 (35)	317 (44)
Teaching	27 (10)	26 (12)	52 (7)
Health associates	20 (7)	10 (5)	49 (7)
Administrative	17 (6)	13 (6)	52 (7)
Business	11 (4)	5 (2)	28 (4)
Management	6 (2)	11 (5)	14 (2)
Other	64 (22)	55 (27)	166 (24)
Missing responses	11 (4)	16 (8)	34 (5)
Current paternal occupation			
Management	29 (11)	21 (10)	90 (13)
Engineering	25 (9)	16 (8)	54 (8)
Business	19 (7)	16 (8)	58 (8)
Construction	18 (7)	12 (6)	38 (5)
IT	16 (6)	18 (9)	46 (6)
Other	116 (44)	102 (47)	325 (46)
Missing responses	44 (16)	25 (12)	101 (14)

*Mean age of participants reported by Whiteley[10] (p. 6) were: autism = 5.49 years; AS = 6.72 years; ASD = 4.76 years. For maternal occupations the following codings have been applied: Teaching = SOC231 (Teaching professionals), Health associates = SOC321 (Health associate professionals), Administrative = SOC413 (Administrative occupations: records), Business = SOC353 (Business and finance associate professionals), Management = SOC113 (Functional managers). For paternal occupations the following codings have been applied: Management = SOC113, Engineering = SOC212 (Engineering professionals), Business = SOC353, Construction = SOC531 (Construction trades), IT = SOC213 (Information and communication technology professionals).

[a]Significant results of ANOVA: mean age (years) $F = 90.756$; d.f. = 2; $P < 0.0005$.

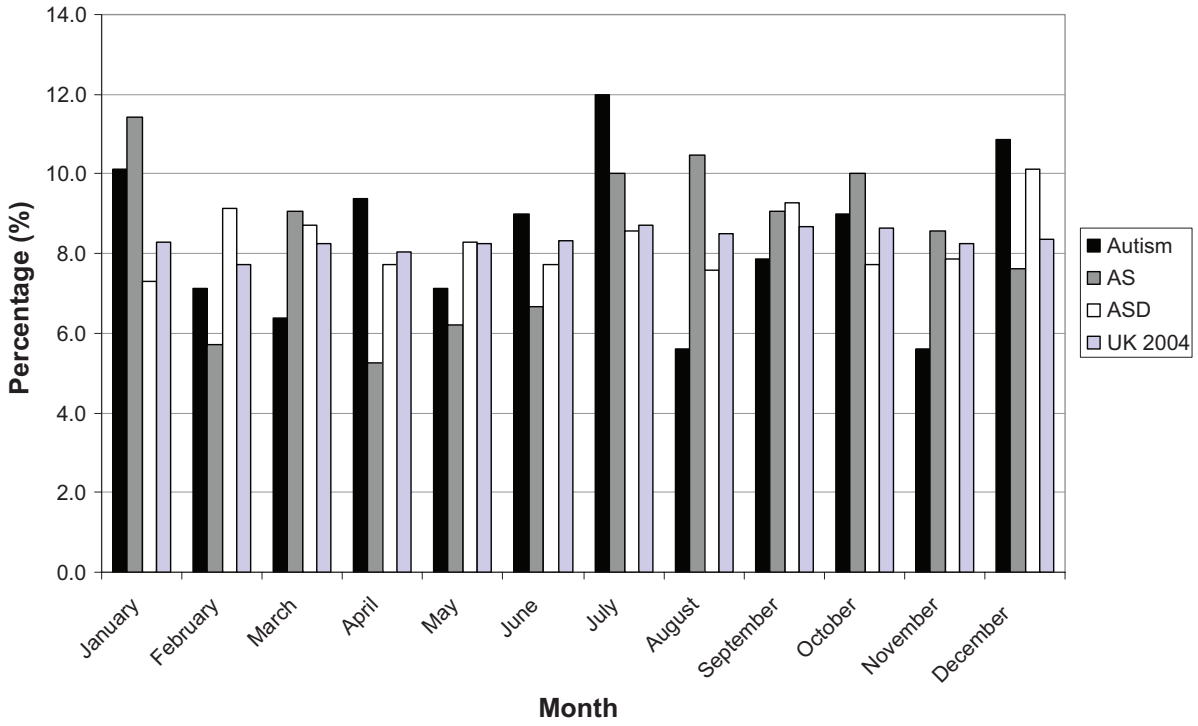

Figure 1. Month of birth according to PDD diagnostic sub-group including UK population birth trends per month for 2004[a].
[a]Data available from the Office for National Statistics (ONS) (Births 1938–2004). http://www.statistics.gov.uk/STATBASE/xsdataset.asp?More=Y&vlnk=4237&All=Y&B2.x=102&B2.y=9.

made by the diagnosing clinician/s. Details of the volume and type of supplementary evidence provided are shown in Table 2. Where supplementary evidence was provided, authors used this as confirmation of parental reporting accuracy of diagnosis. Independent confirmation of diagnoses and/or cognitive abilities was not performed by the authors.

Various additional background data on parents and children were also collected including details of whether the child was fostered or adopted, and confirmation of parental ethnicity. This ensured accurate reporting of gestation and early developmental history and adequate use of English as the primary familial language. For items relating to early infantile history (pregnancy, birth, post-natal period), parents were asked to consult their child's baby development book to aid accurate recall for relevant questions. Maternal and parental occupational responses were subsequently coded by the authors using the Standard Occupational Classification 2000 (SOC2000) schedule.[15]

Statistical analyses were performed using SPSS for Windows™ (version 14.0.1, SPSS, Chicago, IL, USA, 2005). Chi-squared (χ^2) was used for categorical data responses and an analysis of variance (ANOVA) for continuous variables with a significance level for probability (P) set at 0.01. The Ethics Committee at the University of Sunderland had approved all protocols. All data collected were held in accordance with the 1998 Data Protection Act.

Results

Tables 1–9 show the results of the analyses carried out on the current dataset. Items also included as part of the analysis by Whiteley[10] have been marked by a (*). No significant differences in birth month (χ^2 = 23.482; d.f. = 22; P = 0.375; Fig. 1), area of residence (urban, suburban, rural), parental ethnicity or parental occupations were found between the groups (Table 1). Mean age at testing was significantly different between the groups; although showing equivalence with findings previously reported by Whiteley.[10]

Analysis of maternal and paternal occupations based on SOC2000 showed that aside from working at home, the most commonly occurring maternal occupations across the diagnostic groups related to teaching, nursing and administrative vocations. For fathers, management, engineering and business-related jobs were similarly most prevalent. Table 2 details further

Table 2. Details of diagnosis, co-morbidities and pharmacotherapeutic usage of participants according to PDD sub-groups. For *most common assessment instruments* parentheses show percentages according to numbers providing additional evidence of diagnosis. In all other cases parentheses show percentages according to sub-group totals.

	Autism	AS	ASD
Mean age at diagnosis (months)[a]	45.91	75.19	46.37
SD	18.53	26.22	17.80
Co-morbid diagnoses			
Learning disability	2 (1)	–	2 (–)
AD(H)D	4 (1)	13 (6)	12 (2)
DCD/Dyspraxia	–	4 (2)	4 (1)
Epilepsy/Seizures	24 (9)	11 (5)	50 (7)
Supplementary evidence of diagnosis[b]	90 (34)	97 (46)	241 (34)
Most common assessment instruments			
ADOS-G	15 (17)	6 (6)	25 (10)
ADI-R	3 (3)	2 (2)	10 (4)
CARS	7 (8)	–	6 (2)
DISCO	4 (4)	7 (7)	15 (6)
Genetic testing carried out[c]	88 (33)	30 (14)	216 (30)
Down syndrome	1 (–)	–	1 (–)
Tuberous sclerosis	–	–	1 (–)
Fragile X syndrome	–	–	3 (–)
Other genetic condition	5 (2)	3 (1)	6 (1)
Pharmacotherapy usage	63 (24)	58 (28)	155 (22)
Anti-epileptics	6 (2)	2 (1)	15 (2)
Anti-depressants	1 (–)	–	–
Neuroleptics/antipsychotics	2 (1)	–	3 (–)
Stimulants	2 (–)	8 (4)	5 (1)
Hypnotics/sleep-inducers	9 (3)	3 (1)	21 (3)
Sleeping problems	144 (54)	118 (56)	342 (48)
Insomnia[d]	22 (8)	42 (20)	73 (10)
Night waking[e]	90 (34)	33 (16)	209 (29)
Excessive sweating[f]	26 (10)	53 (25)	105 (15)
Indications of nightmare[g]	12 (4)	26 (12)	50 (7)

[a]Significant results of ANOVA: mean age at diagnosis (months) $F = 186.653$; d.f. = 2; $P < 0.0005$. [b]Significant results of χ^2-test: additional evidence of diagnosis $\chi^2 = 11.505$; d.f. = 2; $P = 0.003$. [c]Significant results of χ^2-test: genetic testing carried out $\chi^2 = 24.433$; d.f. = 2; $P < 0.0005$. [d]Significant results of χ^2-test: insomnia $\chi^2 = 18.951$; d.f. = 2; $P < 0.0005$. [e]Significant results of χ^2-test: night waking $\chi^2 = 23.812$; d.f. = 2; $P = 0.003$. [f]Significant results of χ^2-test: excessive sweating $\chi^2 = 22.435$; d.f. = 2; $P < 0.0005$. [g]Significant results of χ^2-test: indications of nightmares $\chi^2 = 10.866$; d.f. = 2; $P = 0.004$.
Abberviations: AD(H)D, Attention-Deficit (Hyperactivity) Disorder; DCD, Developmental Co-ordination Disorder; ADOS-G, Autism Diagnostic Observation Schedule-Generic; ADI-R, Autism Diagnostic Interview-Revised; CARS, Childhood Autism Rating Scale; DISCO, Diagnostic Interview of Social and Communication Disorders.

information on co-morbidity (psychiatric and genetic disorders), the most popular assessment instruments used to make a PDD diagnosis and common pharmacotherapies in current usage amongst the groups.

A significant difference in mean age at diagnosis between the sub-groups was found (Table 2); the average age for the AS group being approximately 30 months later than for the autism and ASD groupings. Significantly more parents of participants with AS also provided supplementary diagnostic information. The use of genetic screening as part of the diagnostic process (to rule out known genetic

Table 3. Categorical time reports of symptom onset and first indications of problems by parents according to diagnostic sub-group. Parentheses show percentages according to sub-group totals.

	Autism	AS	ASD
*Categorical time of symptom onset			
*First 6 months	22 (8)	24 (11)	59 (8)
*7–11 months	21 (8)	22 (11)	64 (9)
*12–15 months	55 (21)	22 (11)	129 (18)
*16–24 months[a]	117 (44)	53 (25)	295 (41)
*Post 24 months[b]	49 (18)	83 (40)	156 (22)
*Missing responses	3 (1)	5 (2)	8 (1)
First indication of problems			
Language problems[c]	95 (36)	17 (8)	280 (39)
Eye contact problems[d]	26 (10)	7 (3)	76 (11)
Behavioral problems[e]	27 (10)	91 (43)	109 (15)
Other	28 (11)	28 (13)	92 (13)
Missing responses	98 (37)	72 (34)	206 (29)

[a]Significant results of χ^2-test: time of symptom onset 16–24 months $\chi^2 = 20.135$; d.f. = 2; $P < 0.0005$. [b]Significant results of χ^2-test: time of symptom onset post 24 months $\chi^2 = 35.639$; d.f. = 2; $P < 0.0005$. [c]Significant results of χ^2-test: language problems $\chi^2 = 85.824$; d.f. = 2; $P < 0.0005$. [d]Significant results of χ^2-test: eye contact problems $\chi^2 = 9.960$; d.f. = 2; $P = 0.007$. [e]Significant results of χ^2-test: behavioral problems $\chi^2 = 121.339$; d.f. = 2; $P < 0.0005$.

conditions) was less frequently reported for the AS group. Analysis of reports of overall sleeping problems between the sub-groups showed no significant difference. Specific items such as insomnia, excessive sweating during sleep and indications of nightmare were however identified as being significantly more frequent for the Asperger syndrome (AS) group than other sub-groupings, whilst episodes of night waking were reduced.

Analysis of items relating to the timing of symptom onset (Table 3) showed some inconsistency with previously reported findings; where no significant difference in temporal categorical bandings was previously reported.[10] In the current dataset, parents of children with AS were significantly more likely to report a later symptom onset (especially post-24 months) than the autism or ASD group. This finding is confirmed where parents had indicated a specific age of symptom onset in months. The mean ages for the groups were: autism ($n = 97$) 18.7 months (SD = 10.4), Asperger syndrome ($n = 67$) 24.1 months (SD = 13.3) and ASD ($n = 243$) 18.2 months (SD = 7.8). Analysis of responses using an ANOVA showed a significant difference between groups (F = 9.898; d.f. = 2; $P < 0.0005$) despite a reduction in responses to this item. Parents of children with AS were also more likely to report overt behavioral problems as being the first indicator of symptom onset rather than the more communicative items (language, eye contact) compared to other groups (Table 3).

Table 4 shows data regarding skills acquired prior to symptom onset, and details significant differences in items such as repeated use of single words (aside from 'mummy' and 'daddy'), the use of 2–3 word phrase speech, pointing to express interest or show something and potty training. Again the AS group showed increased acquisition of all these skills. The AS group also showed a significantly lower frequency of regression in acquired skills in agreement with the findings by Whiteley.[10] Where there was an indication of a loss of previously acquired skills, the mean age values at which regression was reported were: autism ($n = 112$) 20.5 months (SD = 9.3) Asperger syndrome ($n = 58$) 29.2 months (SD = 15.9) and ASD ($n = 280$) 21.7 months (SD = 11.2). Analysis of responses using an ANOVA showed a significant difference between groups (F = 12.426; d.f. = 2; $P < 0.0005$). Current functioning and behavior (Table 5) followed traditional clinical guidelines, with the AS group presenting with a significantly increased use of functional language in comparisons to other sub-groups. A greater frequency in the report of obsessions was also noted for this

Table 4. Skills acquired prior to symptom onset and reports of regression per diagnostic sub-grouping. Percentages as a function of total participants per sub-grouping are shown in parentheses. Percentages for *Skills regressed* are shown as a function of the number of participants who are reported to have shown a regression in acquired skills (autism = 146, Asperger syndrome = 76, ASD = 337).

	Autism	AS	ASD
*Skills acquired prior to symptom onset			
Repeated use of single words (aside from "Mummy", "Daddy")[a]	104 (39)	107 (51)	263 (37)
*Language (2–3 word phrases)[b]	60 (23)	110 (52)	142 (20)
*Pointing to express interest or show something[c]	79 (30)	106 (51)	223 (31)
*Potty training[d]	30 (11)	72 (34)	60 (8)
*Social interest/responsiveness	128 (48)	105 (50)	298 (42)
Crawling	153 (57)	115 (55)	429 (60)
*Walking	197 (74)	149 (71)	498 (70)
*Regression in acquired skills[e]	146 (55)	76 (36)	337 (47)
Skill regressed			
Language regression[f]	93 (64)	27 (35)	239 (71)
Eye-contact[g]	85 (58)	31 (41)	183 (54)
Use of pointing[h]	43 (29)	8 (10)	92 (27)
Social interest[i]	85 (58)	30 (39)	205 (61)
Bladder continence	10 (7)	10 (13)	21 (6)
Bowel continence	15 (10)	16 (21)	34 (10)
Walking	6 (4)	5 (7)	14 (4)

*Significant items reported by Whiteley[10] (p. 7) for skills acquired prior to symptom onset were: language (2 or 3 word phrases), potty training and a regression in acquired skills.
[a]Significant results of χ^2-test: repeated use of single words $\chi^2 = 18.137$; d.f. = 2; $P < 0.0005$. [b]Significant results of χ^2-test: use of 2–3 word phrases $\chi^2 = 90.542$; d.f. = 2; $P < 0.0005$. [c]Significant results of χ^2-test: pointing $\chi^2 = 29.570$; d.f. = 2; $P < 0.0005$. [d]Significant results of χ^2-test: potty training $\chi^2 = 93.813$; d.f. = 2; $P = 0.007$. [e]Significant results of χ^2-test: regression in acquired skills $\chi^2 = 22.005$; d.f. = 2; $P < 0.0005$. [f]Significant results of χ^2-test: language regression $\chi^2 = 36.671$; d.f. = 2; $P < 0.0005$. [g]Significant results of χ^2-test: eye contact $\chi^2 = 18.881$; d.f. = 2; $P < 0.0005$. [h]Significant results of χ^2-test: use of pointing $\chi^2 = 18.165$; d.f. = 2; $P < 0.0005$. [i]Significant results of χ^2-test: social interest $\chi^2 = 21.502$; d.f. = 2; $P < 0.0005$.

group. Both these findings confirm the results presented by Whiteley.[10]

Analyses of somatic items are shown in Tables 6–9. The AS group were reported to show significantly elevated rates of contracting varicella (chicken pox) compared to the other sub-groups. Several other, more general, somatic factors also showed differences; specifically in relation to 'redness of ears' and the appearance of dark circles under the eyes. Frequency of bowel problems and functional bowel habits are detailed in Table 7. Unsurprisingly, rates of achievement of bowel and bladder continence (both day and night) were significantly higher for the more able AS group. Overall, 48% of the total group (autism, AS and ASD) were reported to show problems with functional bowel habits; with constipation reported in 23% of the group. The AS sub-group were described as showing a more frequent indication of abdominal pain; although no other significant bowel symptoms such as bloating or distension were found to be confirmatory in comparison to the other groups. In terms of bowel habits, the majority of participants tended to produce stools indicative of normal bowel habits (snake-like smooth, fluffy with ragged edges, soft blobs with clear edges) rather than lumpy or loose stools; although about a fifth of all participants produced large, bulky stools. In terms of bowel habit problems, the autism group showed a significantly increased frequency of undigested food present in stools.

Table 5. Reported frequency of current skills per diagnostic sub-grouping. Parentheses show percentages as a function of sub-group totals.

	Autism	AS	ASD
*Categorical current language[a]			
*No current use of language	71 (27)	1 (–)	125 (18)
Use of single words only (not including "mummy", "daddy")	58 (22)	–	144 (20)
*Use of 2–3 word phrase speech	123 (46)	192 (91)	418 (59)
Missing responses	15 (6)	17 (8)	25 (3)
*Current behavior			
*Presence of routines/rituals (compulsive in nature)	172 (64)	136 (65)	418 (58)
Missing responses (routines)	14 (5)	14 (7)	23 (3)
*Obsessions[b]	158 (59)	180 (86)	457 (64)
Missing responses (obsessions)	12 (4)	5 (2)	31 (4)

*Significant items reported by Whiteley[10] (p. 8) for current skills variables were: categorical current language and the presence of obsessions. [a]Significant results of χ^2-test: current language $\chi^2 = 138.845$; d.f. = 6; $P < 0.0005$. [b]Significant results of χ^2-test: obsessions $\chi^2 = 41.199$; d.f. = 2; $P < 0.0005$.

Rates of skin and respiratory complaints are reported in Table 8 with 39% of the total group presenting with a history of eczema or contact dermatitis. A history of the bacterial skin disorder impetigo was more frequently reported for the AS group; as was a history of fungal infection leading to athletes foot. A history of asthma was also more frequently noted for the AS group.

Table 9 details pre-, peri- and post-natal events per sub-group. Approximately 5% of all parents reported use of some artificial or aided methods of conception. Other notable details were reports of fetal distress and emergency caesarean delivery present in approximately 20 and 25% of all participants respectively. Where there was information about the number of weeks gestation at delivery, the mean values were: autism ($n = 143$) 39.0 weeks (SD = 3.1), Asperger syndrome ($n = 140$) 39.0 weeks (SD = 2.7) and ASD ($n = 457$) 38.8 weeks (SD = 2.6). Mean birth weights were: autism ($n = 50$) 3385.98 g (SD = 662.7), Asperger syndrome ($n = 57$) 3414.21 g (SD = 633.2) and ASD ($n = 238$) 3315.32 g (SD = 712.2). Mean birth lengths were: autism ($n = 73$) 50.78 cm (SD = 7.1), Asperger syndrome ($n = 84$) 51.80 cm (SD = 8.6) and ASD ($n = 277$) 50.69 cm (SD = 6.9). There were no significant differences amongst any of these variables between the groups. Breastfeeding rates (exclusively >4 weeks) were high for all groups (60%–69%) in comparisons to contemporary UK population statistics for the first month (≈55%).[16] A significant difference in rates of reported early infantile feeding problems was found for the AS group in agreement with result from Whiteley.[10] The exact types of feeding problems were not however elucidated by any significant diagnostic difference in specific items measured (vomiting, projectile vomiting, colic, failure to feed or reflux).

Discussion

The overlap between the presented results and those independently reported by Whiteley[10] suggests a degree of consistency in the behavioral and somatic trends being detailed by parents of participants diagnosed with PDD using the parent-report method. The appearance of differences in developmental and behavioral factors particularly in relation to Asperger syndrome (AS) compared to the other sub-groupings, match expected differences in the development and presentation of clinical symptoms centered on the severity of symptoms displayed in connection with language and behavior. On that basis, the methods employed by the authors using parents as primary informers alongside secondary, confirmatory evidence gains credibility. The various somatic factors identified as significant

Table 6. Frequency of reported viral infections, ear/hearing problems and eye/vision problems per diagnostic sub-grouping. Parentheses show percentages as a function of sub-group totals.

	Autism	AS	ASD
*History of viral infection			
Encephalitis	2 (1)	–	2 (–)
Meningitis	3 (1)	2 (1)	6 (1)
*Varicella[a]	128 (48)	131 (62)	355 (50)
*Measles	6 (2)	9 (4)	12 (2)
*Mumps	3 (1)	1 (1)	2 (–)
**Rubella*	2 (1)	5 (2)	8 (1)
Other	40 (15)	28 (13)	102 (14)
History of ear problems			
Hearing loss	29 (11)	18 (9)	40 (6)
*Recurrent ear infection (otitis)	58 (22)	51 (24)	141 (20)
Redness of ears[b]	71 (27)	82 (39)	180 (25)
*Use of grommets/tubes	38 (14)	21 (10)	82 (12)
Glue ear/blockage	10 (4)	4 (2)	24 (3)
History of eye/vision problems			
Loss of sight in both eyes	–	–	1 (–)
Loss of sight in one eye	2 (1)	2 (1)	–
Use of peripheral vision	21 (8)	7 (3)	68 (10)
Dark rings around the eyes[c]	72 (27)	85 (40)	195 (27)
Squint	31 (12)	16 (8)	58 (8)
Myopia	2 (1)	3 (1)	4 (1)
Presbyopia	2 (1)	7 (3)	10 (1)

Varicella—chicken pox; myopia—near-sightedness; presbyopia—loss of flexibility in crystalline lens of the eye.
[a]Significant results of χ^2-test: history of viral infection—varicella $\chi^2 = 12.280$; d.f. = 2; $P = 0.002$. [b]Significant results of χ^2-test: redness of ears $\chi^2 = 15.585$; d.f. = 2; $P < 0.0005$. [c]Significant results of χ^2-test: dark rings around the eyes $\chi^2 = 14.481$; d.f. = 2; $P = 0.001$.

differentiators in both studies, particularly in connection to the AS group, likewise gather merit; this, despite no confirmatory clinical investigation of symptoms being carried out in the current investigation.

As per the findings of Whiteley,[10] there was a significant difference in the age of participants between the various PDD sub-groups, with the AS group presenting at an older mean age than the other groupings. A robust explanation for this difference can be found in the developmental and behavioral data obtained during the current study. This suggested that in comparison to the autism and ASD groups, the AS cohort presented with a later time of symptom onset, less indications of early problems in core areas such as language and eye contact, an increased likelihood of achieving normal developmental milestones prior to diagnosis and fewer reports of regression in previously acquired skills. The accompanying finding of a significant difference in mean age at diagnosis between the groups (Table 2) is also supportive and consistent with other findings reporting disparity.[17] These observations combined with findings of wide variations in current language skills (Table 5) according to diagnostic groups; the AS group almost unanimously presenting with 2–3 word phrase speech in comparison to the other sub-groups, although also presenting with significantly more behavioral problems such as obsessionality. This would tend to show agreement with other clinical descriptions of Asperger syndrome where communication in the form of syntactical speech are reported as normal in comparison to autism.[18]

Table 7. Frequency of reported bowel habits and problems per diagnostic sub-grouping. Parentheses show percentages as a function of sub-group totals.

	Autism	AS	ASD
*Full bladder continence achieved[a]	124 (46)	166 (79)	344 (48)
*Full bowel continence achieved[b]	121 (45)	188 (89)	361 (51)
*Problem with bowel habits present	125 (47)	119 (57)	327 (46)
*Diarrhea	44 (16)	34 (16)	105 (15)
*Constipation	61 (23)	58 (28)	157 (22)
*Alternating diarrhea/constipation	43 (16)	41 (19)	104 (15)
*Undigested food in stools[c]	50 (19)	23 (11)	82 (11)
*Blood in stools	7 (3)	9 (4)	17 (2)
*Mucus in stools	26 (10)	13 (6)	63 (9)
Type of stool reported			
S1. Separate hard lumps (nut like)	55 (21)	37 (18)	164 (23)
S2. Sausage shaped and lumpy	54 (20)	41 (19)	147 (21)
S3. Sausage shaped with cracks	30 (11)	37 (18)	109 (15)
S4. Snake-like smooth	92 (34)	74 (35)	230 (32)
S5. Soft blobs with clear edges	27 (10)	17 (8)	64 (9)
S6. Fluffy with ragged edges	61 (23)	50 (24)	157 (22)
S7. Watery with no solids	33 (12)	12 (6)	64 (9)
Frothy stools	15 (6)	7 (3)	27 (4)
Large, bulky stools	47 (18)	42 (20)	123 (17)
Other stools NOS	29 (11)	8 (4)	70 (10)
Manual help with defecation	16 (6)	11 (5)	41 (6)
General color of stools			
Light brown	146 (55)	95 (45)	375 (53)
Dark brown	104 (39)	83 (39)	291 (41)
Black stools	12 (4)	5 (2)	28 (4)
Yellow, sand coloured	67 (25)	38 (18)	182 (26)
Green stools	18 (7)	6 (3)	36 (5)
Number of bowel movements			
1 per week	4 (1)	6 (3)	12 (2)
2 per week	8 (3)	5 (2)	18 (2)
3 per week	10 (4)	12 (6)	32 (4)
4 per week	23 (9)	13 (6)	59 (8)
5–15 per week	128 (48)	102 (49)	369 (52)
More than 15 per week	23 (9)	8 (4)	62 (9)
Missing responses	71 (27)	63 (30)	159 (22)

(*Continued*)

Table 7. (*Continued*)

	Autism	AS	ASD
Other bowel problems			
Bloating	37 (14)	29 (14)	80 (11)
Distension (pot-bellied)	65 (24)	44 (21)	167 (23)
Indications of pain on passing stools	37 (14)	46 (22)	121 (17)
Indications of abdominal pain[d]	50 (19)	68 (32)	136 (19)
Flatulence (frequent wind)	69 (26)	65 (31)	191 (27)

NOS—Not Otherwise Specified. Types of stool reported show the 7 categories of stool based on the Bristol Stool Chart[33] (S1–S7). Stools S1 and S2 indicate constipation, S3 and S4 indicate the ideal stool, S5-S7 show a tendency towards diarrhea or urgency.
*Significant items reported by Whiteley[10] (p. 8) for clinical features variables were: achievement of bowel and bladder continence. No other details on functional bowel habits were provided.
[a]Significant results of χ^2-test: full bladder continence achieved $\chi^2 = 67.164$; d.f. = 2; $P < 0.0005$. [b]Significant results of χ^2-test: full bowel continence achieved $\chi^2 = 113.608$; d.f. = 2; $P < 0.0005$. [c]Significant results of χ^2-test: undigested food in stools $\chi^2 = 9.840$; d.f. = 2; $P = 0.007$. [d]Significant results of χ^2-test: indications of abdominal pain $\chi^2 = 22.949$; d.f. = 2; $P < 0.0005$.

The results suggest that a diagnosis of AS, in particular, may potentially confer an increased susceptibility to a number of somatic conditions not previously linked to clinical definitions of symptoms. That being said we are not able to rule out a purely epiphenomenal relationship to such conditions at this time. There also remains a degree of controversy regarding the nosological validity of Asperger syndrome (AS) as a distinct clinical condition. Despite incorporation into the most recent diagnostic classification systems, debate still continues as to whether AS is truly distinguishable from autism associated with higher levels of cognitive ability.[19] Diagnosis of AS is normally hierarchical rather than explicit. Exclusion of other conditions such as childhood autism is first undertaken and, assuming that other criteria are not met, for schizophrenia for example, so AS is diagnosed. Asperger's original description of the condition[5] did not decree specific diagnostic criteria. This combined with the relatively late arrival of AS as a formal diagnostic entity into clinical classifications has led to a number of alternative schedules being developed. Comparisons of some of these schedules[20] with more formal diagnostic

Table 8. Frequency of reported skin problems/conditions and respiratory problems/conditions per diagnostic sub-grouping. Parentheses show percentages as a function of sub-group totals.

	Autism	AS	ASD
*History of skin complaints			
*Eczema/contact dermatitis	104 (39)	98 (47)	267 (37)
*Acne	2 (1)	2 (1)	2 (–)
Psoriasis	–	1 (–)	1 (–)
*Athletes foot[a]	3 (1)	14 (7)	11 (1)
*Impetigo[b]	25 (9)	37 (18)	56 (8)
History of respiratory complaints			
Asthma [c]	36 (13)	50 (24)	106 (15)
Wheeze	29 (11)	23 (11)	47 (7)
Hayfever	4 (1)	3 (1)	4 (1)
URTI	11 (4)	8 (4)	16 (2)

URTI—Upper Respiratory Tract Infection. *Significant item reported by Whiteley[10] (p. 8) for clinical features variables is: impetigo.
[a]Significant results of χ^2-test: athletes foot $\chi^2 = 20.770$; d.f. = 2; $P < 0.0005$. [b]Significant results of χ^2-test: impetigo $\chi^2 = 17.326$; d.f. = 2; $P < 0.0005$. [c]Significant results of χ^2-test: asthma $\chi^2 = 11.164$; d.f. = 2; $P = 0.004$.

Table 9. Frequency of pre-, peri-, and post-natal events per diagnostic sub-grouping. Parentheses show percentages as a function of sub-group totals. Percentages for specific items headed under *Infant feeding problems* are shown as a function of the number of participants who were reported to have shown early feeding problems (autism = 103, Asperger syndrome = 118, ASD = 318).

	Autism	AS	ASD
Artificial methods of conception	10 (4)	10 (5)	35 (5)
*Pre- and peri-natal factors			
Maternal infection			
during pregnancy	26 (10)	11 (5)	54 (8)
Gestational diabetes	1 (–)	2 (1)	1 (–)
Hyperemesis Gravidarum	–	1 (–)	4 (1)
High maternal blood pressure	3 (1)	–	10 (1)
*Fetal distress	55 (21)	57 (27)	135 (19)
*Emergency c-section	44 (16)	37 (18)	119 (17)
*Hypoxia/anoxia	8 (3)	5 (2)	14 (2)
*Pre-eclampsia	16 (6)	17 (8)	37 (5)
Breech presentation	6 (2)	5 (2)	20 (3)
Post-natal			
*Jaundice	60 (22)	53 (25)	142 (20)
*Anti-D administered	37 (14)	28 (13)	86 (12)
*Breastfed (>4 weeks)	161 (60)	144 (69)	463 (65)
*Infant feeding problems[a]	103 (39)	118 (56)	318 (45)
Vomiting	27 (26)	32 (27)	83 (26)
Projectile vomiting	23 (22)	17 (14)	41 (13)
Colic	47 (46)	61 (52)	150 (47)
Failure to feed	8 (8)	16 (14)	39 (12)
Reflux	8 (8)	9 (8)	27 (8)
Other problem NOS	8 (8)	13 (11)	45 (14)

Hyperemesis Gravidarum—morning sickness; Anti-D—Anti-D Immunoglobulin D. *Significant item reported by Whiteley (2004a) (p. 8) for pre-, peri- and post-natal events variables is: infant feeding problems.
[a]Significant results of χ^2-test: Infant feeding problems $\chi^2 = 15.170$; d.f. = 2; $P = 0.001$.

systems show both similarities and differences; primarily illustrated by how narrow the concept of AS is defined and how closely they relate to the original descriptions provided by Asperger.[21] Despite nearly half of all participants with AS providing supplementary evidence of diagnosis, none of the most commonly used assessment instruments provided were AS specific.

Examination of the early descriptions for both autism and Asperger syndrome imply that possible co-morbidity with somatic symptoms may not be a new phenomenon. Kanner[4] noted in his original descriptions that several of his patients presented with co-morbid physical ailments such as '*Alfred*' who had often been kept in bed due to "*chickenpox, streptococcus infection* [and] *impetigo*" (p. 234). Indeed, the continued association between AS and the bacterial skin disorder impetigo, predominantly caused by group A beta-hemolytic *Steptoccocus* or *Staphylococcus aureus* remains an interesting finding. Both the current study and the previous results presented by Whiteley,[10] reported a stable incidence of 18% of participants with AS who had a history of infection (although no additional information regarding the type of impetigo, bullous or nonbullous, is available). This figure compares with UK and European estimates

of between 2%–3% for the pediatric population.[22,23] Although the epidemiology of impetigo is still under investigation, factors such as hygiene, seasonality and social factors related to crowding are thought to increase the risk of contracting the bacteria causative of the disease. Improper hand-washing, pica (eating on non-edible substances) and a greater propensity to handling feces (i.e. smearing) are also thought to increase the risk of contracting such infections; behaviors that would not necessarily be associated to any greater degree with the higher-functioning AS group in comparison to the other, more severely affected sub-groups.

The alternative suggestion as to the increased risk of infection for the AS group may lie in differences in the way that the immune system deals with such infections. Several reports on the potential for inherent problems associated with the eradication of viruses and bacteria in PDD have been published.[24] The involvement of the immune system in PDD is complex, with a number of themes emerging centered on autoimmunity, the presence of pro-inflammatory features and immunodeficiency. The primary immune response will tend to be inflammatory; normally focused at the various barriers of the body such as skin, gastrointestinal (GI) tract or lungs where pathogens first gain entry. Given then the additional findings of a significantly increased frequency of inflammatory respiratory conditions such as asthma again with the AS group, one could assume a potential connection may be pertinent.

Several other somatic findings for the AS group also merit similar discussion. Reports indicative of an increased frequency of "redness of the ears" and dark rings around the eyes are important observations, despite not carrying any obvious associated disease state. Dark rings around the eyes could for example become apparent as a function of lack of sleep or poor sleep quality; factors that have been reported specifically in connection to AS.[25] Indeed, insomnia and indications of nightmare were more frequently reported for the AS group alongside reports of excessive sweating during sleep. What is not so easy to deduce from this argument are the findings of significantly reduced levels of night waking amongst the AS group; indicating that whilst initially getting to sleep may be a problem, this group would be less likely to wake frequently during the night and show disturbed sleep patterns. One alternative explanation for the issue of sleep deprivation is again a potential role for the immune system. Several authors have reported on the issue of dark rings under the eyes as being akin to allergic shiners;[26] whereby discoloration under the eyes is representative of atopy or allergic disease. Another possible association relates to the role of sulphate in PDD.[27] In the absence of any corresponding biochemical measures in the current study however, all these possibilities must remain speculative.

Although not fully elucidated, the increased frequency of infantile feeding problems noted for the AS group is another interesting finding. When comparing responses for all three groups on this item, reported early feeding problems actually decrease in frequency according to the expected increasing severity of symptoms by grouping. Previous explanations have been provided for childhood feeding problems including fine motor control problems associated with muscle control of the tongue and mouth.[28] This also fits in with other association made specifically between AS and motor co-ordination disorder such as Developmental Co-ordination Disorder (DCD)/dyspraxia.[6] The issue however is that such explanations have tended to reflect problems with older children who have already been introduced to solid foods.[a] One therefore has to question whether such problems could manifest at an earlier age or whether other factors such as the food provided for the infant, based on either breast- or infant formula milk, may be exerting a potential physiological effect. Research has already begun to implicate the removal of casein (the primary protein of milk) from the diet of children with PDD as being of potential benefit in terms of a reduction of behavioral and somatic symptoms.[29] It may be possible that such early feeding problems are reflective of an underlying allergy or intolerance to such foodstuffs.

In a similar vein, a potential role for gastrointestinal (GI) factors in PDD is still the topic of some debate. Functional GI problems such as constipation and diarrhea tend to be more frequently diagnosed in people with a neurological or learning disability than in asymptomatic populations[30] although no definitive explanation has been provided to account for this finding. Forty-eight percent of the total PDD group in the present study were reported to present with

[a]The questionnaire item used as part of the current study explicitly asks about problems with feeding as a young baby rather than young child.

problems in functional bowel habits, with nearly a quarter (23%) described as having constipation. This contrasts with totals of 20% and 17% respectively from the previous report.[10] No one particular group seemed to demonstrate any distinct pattern of functional bowel habit problems despite individual items based on indications of abdominal pain and undigested food in the stools showing differences.

A number of issues regarding the methodology employed in the current study require comment. Aside from the examination of responses for the PDD sub-groups, we have not included data from any other control group, either based on asymptomatic or learning disabled participants, as potential comparators. Although such investigations were not a primary aim of the study, they would nevertheless have provided important information about responses to the questionnaire items outside of the target group. The basis for study recruitment, as part of related investigations, is another point in question. One cannot guarantee that participants are necessarily representative of the population given the "dietary/biological" focus of the investigations from which the current study is drawn. Indeed, it may have encouraged a disproportionate number of participants to join who share specific views on the role of physiological factors in PDD. Given however, that most of the somatic items reported as being significantly different between the sub-groups will require some form of clinical diagnosis (e.g. impetigo, asthma) and/or pharmacotherapeutic use for treatment, one cannot wholly ascribe results to informant attribution or any societal influences. Future use of proactive, formal clinical diagnostic assessment for such somatic conditions would address such an issue.

The significant difference in chronological age between the PDD sub-groups over the study period combined with a lack of data regarding reported onset for specific somatic factors represent potential sources of bias to our study results. The mean age of the AS group was approximately 1½–2 years older than that of the average age of the other cohorts during the investigation, indicating a greater period of 'risk' time and opportunity for the AS group to develop specific conditions or infections over the other groups. This is particularly true when examining rates of asthma and wheezing illnesse in the general population according to age.[31] To counter this argument, age-specific incidence rates for chickenpox for example, have shown an increased likelihood of contracting the virus between 0–4 years; thereafter declining with increasing age.[32] Age-specific incidence rates for impetigo likewise show the 4–5 year age-group to be most at risk.[23] Peak exposure periods for most somatic items were therefore covered by the participant age ranges included.

The use of parents as primary reporters is always subject to several potential forms of bias. Controlling for country of residence and parental ethnicity as well as using additional evidence of diagnosis and assessment as a confirmation of accuracy, reduces the potential for reporting bias or omissions on the basis of informant characteristics. Whilst problems with retrospective recall can never be ruled out in such study designs, the low mean age of participants at time of information gathering and the finite ceiling age of the sample group also go some way to minimize the potential impact on reporting. The use of an independent sample, large participant numbers combined with a stringent significance threshold of probability ($P < 0.01$) in the current study go some way to balancing out the potential biases that accompany the use of parents as primary information providers.

Conclusion

Parental reporting of the diagnostic sub-groups of PDD provided a number of significant discriminating items concomitant with current clinical diagnostic guidelines and anticipated level of cognitive functioning. The confirmation of additional somatic factors more frequently attributed to a diagnosis of Asperger syndrome suggests the potential for a greater susceptibility to specific physiological problems for patients with this diagnosis outside of diagnostic developmental and behavioral indices. Further clinical investigations are required to rule out a purely epiphenomenal relationship.

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Disclosures

The authors report no conflicts of interest.

References

1. World Health Organisation (WHO). *Tenth revision of the International Classification of Diseases and related health problems. Clinical Descriptions and diagnostic guidelines.* Geneva: WHO; 1992.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* (4th ed.) APA 1994. Washington, DC.
3. Happé F, Ronald A, Plomin R. Time to Give up on a Single Explanation for Autism. *Nature Neuroscience*. 2006;9:1218–20.
4. Kanner L. Autistic Disturbances of Affective Contact. *Nervous Children*. 1943;2:217–50.
5. Asperger H. Die "Autistischen Psychopathen". *Kindesalter Archiv für Psychiatrie und Nervenkrankheiten*. 1944;117:76–136.
6. Green D, Baird G, Barnett AL, Henderson L, Huber J, Henderson SE. The Severity and Nature of Motor Impairment in Asperger's Syndrome: A Comparison with Specific Developmental Disorder of Motor Function. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2002;43:655–68.
7. Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal Autoimmune Diseases, Asthma and Allergies, and Childhood Autism Spectrum Disorders: A Case-Control Study. *Archives of Pediatrics and Adolescent Medicine*. 2005;159:151–7.
8. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial Clustering of Autoimmune Disorders and Evaluation of Medical Risk Factors in Autism. *Journal of Child Neurology*. 1999;14:388–94.
9. Molloy CA, Manning-Courtney P. Prevalence of Chronic Gastrointestinal Symptoms in Children with Autism and Autistic Spectrum Disorders. *Autism*. 2003;7:165–71.
10. Whiteley P. Developmental, Behavioral and Somatic Factors in Pervasive Developmental Disorders: Preliminary Analysis. *Child: Care, Health and Development*. 2004a;30:5–11.
11. Whiteley P, Rodgers J, Shattock P. Clinical Features Associated with Autism: Observations of Symptoms Outside the Diagnostic Boundaries of Autistic Spectrum Disorders. *Autism*. 1998;2:415–22.
12. Whiteley P, Rodgers J, Savery D, Shattock P. A Gluten-free Diet as an Intervention for Autism and Associated Spectrum Disorders: *Preliminary Findings Autism*. 1999;3:45–65.
13. Whiteley P, Dodou K, Todd L, Shattock P. Body Mass Index of UK Children Diagnosed with Pervasive Developmental Disorders. *Pediatrics International*. 2004b;46:531–3.
14. Whiteley P, Waring R, Williams L, et al. Spot Urinary Creatinine Excretion in Pervasive Developmental Disorders. *Pediatrics International*. 2006;48:292–7.
15. Standard Occupational Classification. Office for National Statistics (ONS). Fareham, UK; 2000.
16. Pontin D, Emmett P, Steer C, Emond A; ALSPAC Study Team. Patterns of Breastfeeding in a UK Longitudinal Cohort Study. *Maternal and Child Nutrition*. 2007;3:2–9.
17. Howlin P, Asgharian A. The Diagnosis of Autism and Asperger Syndrome: Findings from a Survey of 770 Families. *Developmental Medicine and Child Neurology*. 1999;41:834–9.
18. Berney T. Asperger Syndrome from Childhood into Adulthood. *Advances in Psychiatric Treatment*. 2004;10:341–51.
19. Schopler E. Are Autism and Asperger syndrome (AS) Different Labels or Different Disabilities? *Journal of Autism and Developmental Disorders*. 1996;26:109–10.
20. Ehlers S, Gillberg C, Wing L. A Screening Questionnaire for Asperger Syndrome and Other High-functioning Autism Spectrum Disorders in School Age Children. *Journal of Autism and Developmental Disorders*. 1999;29:129–41.
21. Leekam S, Libby S, Wing L, Gould J, Gillberg C. Comparison of ICD-10 and Gillberg Criteria for Asperger Syndrome. *Autism*. 2000;4:11–28.
22. McCormick A, Fleming D, Charlton J. Morbidity Statistics from General Practice. Fourth National Study 1991–1992, 1995; Office of Population Censuses and Surveys.
23. Koning S, Mohammedamin RS, van der Wouden JC, van Suijlekom-Smit LW, Schellevis FG, Thomas S. Impetigo: Incidence and Treatment in Dutch General Practice in 1987 and 2001-Results from Two National Surveys. *British Journal of Dermatology*. 2006;154:239–43.
24. Warren RP, Singh VK, Averett RE, et al. Immunogenetic Studies in Autism and Related Disorders. *Molecular and Chemical Neuropathology*. 1996;28:77–81.
25. Paavonen EJ, Vehkalahti K, Vanhala R, von Wendt L, Nieminen-von Wendt T, Aronen ET. Sleep in Children with Asperger Syndrome. *Journal of Autism and Developmental Disorders*. 2007;38:41–51.
26. Marks MB. Recognizing the Allergic Person. *American Family Physician*. 1977;16:72–9.
27. Waring RH, Klovrza LV. Sulphur Metabolism in Autism. *Journal of Nutritional and Environmental Medicine*. 2000;10:25–32.
28. Wing L. *The Autistic Spectrum.* London: Constable; 1996.
29. Lucarelli S, Frediani T, Zingoni AM, et al. Food Allergy and Infantile Autism. *Panminerva Medica*. 1995;37:137–141.
30. Bohmer CJ, Taminiau JA, Klinkenberg-Knol EC, Meuwissen SG. The Prevalence of Constipation in Institutionalized People with Intellectual Disability. *Journal of Intellectual Disability Research*. 2001;45:212–8.
31. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *British Medical Journal*. 1996;312:1195–9.
32. Lowe G, Salmon R, Thomas D, et al. Declining incidence of chickenpox in the absence of universal childhood immunisation. *Archives of Disease in Childhood*. 2004;89:966–9.
33. Lewis SJ, Heaton KW. Stool form scales as a useful guide to intestinal transit time. *Scandinavian Journal of Gastroenterology*. 1997;32:920–4.