TITLE:

COHORT PROFILE: THE ISLE OF WIGHT WHOLE POPULATION BIRTH COHORT (IOWBC)

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Why was the cohort set up?

By the late 1980s, it was clear that allergic diseases, including asthma, eczema, allergic rhinitis and food allergy, had been increasing in recent decades, but the extent of this increase and true prevalence in an unselected population had not been estimated. It was also known that allergic diseases may remit and relapse. So while one disease improves as the child grows, another may take its place; this pattern was termed "atopic or allergic march". However, the extent and the true nature of this transition was not clear. Additionally, little was known why allergic diseases are increasing and even less about why allergic disease often remits as the child grows, but sometimes relapses in adolescent or adult life. We therefore established the Isle of Wight Birth Cohort (IOWBC) 28 years ago, in January 1989.

The Isle of Wight is an island off the south coast of England with a resident population of approximately 130,000. The environment is semirural with no heavy industry and the local economy largely relies on tourism.

The focus of the IOWBC is to:

- Assess prevalence of allergic sensitisation and clinical allergic manifestations in an unselected population during childhood and early adult life.
- Explore the natural history of allergic sensitisation and clinical allergic manifestations from infancy to early adult life.
- Define the heterogeneity of asthma and allergic diseases across the life course.
- Identify predictive markers for asthma and allergy development that might guide future disease prevention or treatment measures.
- Develop novel therapeutic interventions.
- Identify environmental risk factors relevant to asthma and allergic diseases.

- Investigate genes, gene-environmental interactions and epigenetic mechanisms in the development of asthma and other allergic diseases.

The IOWBC was originally established with support from the local (Isle of Wight) Health Authority, who helped establish the cohort and the assessments at ages 1, 2 and 4 years. A grant from the charity 'Asthma UK' allowed assessment at age 10 years. Further funding from the National Institutes of Health (US) and the Medical Research Council (UK) has supported the cohort up to the most recent assessment at 26 years.

Who is in the cohort?

Recruitment: The IOWBC is a single centre study designed to represent the community population. All children born on the Isle of Wight in a defined period were eligible for inclusion. Ethics approval was obtained from the local/National Ethics Committees at recruitment of the birth cohort between January 1989 and February 1990, and subsequently at each assessment. The cohort was recruited through the 1509 women who gave birth to 1536 children on the IOW during the recruitment period. All 1509 mothers were recruited and consented to complete questionnaires and provide samples soon after birth. Parental consent was obtained from 1456 of the 1536 children for inclusion into a longitudinal study of asthma and allergic disease. (Figure 1)

How often have they been followed up?

The children in the IOWBC have been seen on 6 occasions over the course of 26 years, at 1, 2, 4, 10, 18 and 26 years (Table 1). Extremely high retention rates have been obtained at all-time points. Cohort particpants who attended or did not attend at various assessments were compared for information collected at birth when parents of all 1536 infants responded and provided basic information on family history of allergy, birth weight, social status and exposures to pets and smoking (Table 2).

What has been assessed and/or measured?

Hospital records were used to gather information on maternal height and weight at week 14 (±4) of gestation, pregnancy characteristics and complications, and birth characteristics. A sample of maternal blood and cord blood at birth and children's blood from a heel prick was collected at 7 days of age on Guthrie cards.

Questionnaires, both study specific and standardised questionnaires (International Study of Asthma and Allergic Diseases in Childhood from 10 years onwards when these became available) seeking information on asthma and allergy status and common environmental exposures were completed by most participants or their parents at various assessments throughout childhood and early adult life (Table 3). Mothers completed a questionnaire soon after the birth of her child (Table 4), and at one and two years, children were seen by a doctor, nurse or health visitor and a questionnaire completed. If parents reported any allergy related symptoms in their child, they were asked to attend the clinic for a visit where examination and allergy skin prick tests (SPT) were carried out. Physical examination at all assessments included height, weight, and signs of allergic diseases such as wheeze and eczema. At 4, 10, 18 and 26 years, all participants were invited to attend the research centre for an assessment, which included questionnaire, physical examination, and skin prick test. At 10, 18 and 26 years, spirometry and bronchial provocation tests were carried out and blood and urine samples were collected. Exhaled nitric oxide was measured at 18 and 26 years. A subgroup of children were invited for sputum induction at 10 and 18 years. At all ages, those who could not attend the centre for a personal visit were asked to complete a telephone or postal questionnaire. At 26 years, on-line questionnaires were first introduced, in addition to telephone and postal questionnaires, to achieve optimal participation. Where possible, participants were asked to give permission for access to their medical records, which provided more accurate data regarding physician diagnosis and treatments given.

Serum total IgE was measured at birth (in the cord serum), and again at 10 and 18 years. Specific IgE screens for aero and food allergens were carried out at 10 and 18 years. Serum leptin and urinary cotinine were measured at 10 and 18 years. In a subgroup, a panel of cytokines was measured at 10 and 18 years. Genome-wide genotyping is being carried out currently and data will be available shortly. Genome-wide epigenotyping with DNA methylation was carried out in a subgroup of participants in whole-blood derived DNA collected at 18 years and is now being extended to all participants with blood samples available at birth (using Guthrie cards), and 10 and 18 years.

What has it found?

Nearly 100 original articles have been published, describing prevalence, natural history and genetic and environmental risk factors for asthma and allergic diseases up to 18 years of age, while data collected at the age of 26 years are currently being analysed. A list of publications arising from the IOWBC can be found at http://www.allergyresearch.org.uk.

Prevalence

We described the population prevalence of allergic disorders at various ages in this unselected birth cohort. The prevalence was generally described as period prevalence, i.e. in the last 12 months at each assessment. We used study-specific questionnaires in the first 3 assessments and later repeated these questionnaires as well as using standardised International Study of Asthma and Allergy in Childhood (ISAAC) questionnaires[1], which had become available between the 4 and 10 year follow-up. The overall prevalence of one or more allergic disease varied from ~25% in the first 2 years to 40% at 4 and 50% by the age of 18 years.[2-6]

Asthma. Reported asthma at 1, 2 and 4 years, defined as recurrent wheezing, increased from 8.7% at 1 years to 14.9% at 4 years.[2,4,7] At age 10, 18 and 26 years, we characterised cohort children

extensively for asthma and allergic diseases using standardized questionnaires, lung function, bronchial provocation tests, and sputum induction.[5,6,8-11] We also described wheezing phenotypes during the first 10 years of life, identifying that more severe disease had an early onset and could be distinguished from more transient disease using risk scoring systems .[8,9,12,13] We investigated early life risk factors for the development of asthma and bronchial hyper responsiveness (BHR) during later childhood[10,13] and how these factors influence symptom expression in those with BHR[10] and induce earlier onset of disease.[14]

Nearly 5% of adolescents reported wheezing in the absence of diagnosed asthma and showed few pathophysiological hallmarks of asthma. This 'undiagnosed wheeze' phenotype was associated with smoking and paracetamol use.[15] Applying cluster analysis methods on IOWBC data, we have defined wheeze and rhinitis clusters to explore phenotypes of these conditions using adolescents.[16,17] By 18-years severe asthma clusters with evidence of impaired lung function, high morbidity and higher smoking prevalence were identifiable.

Allergic rhinitis. Rhinitis was defined as nasal and/or eye symptoms of sneezing, rhinorrhoea, nasal blockage, and streaming/itchy eyes when not having a "cold" or respiratory infection. At 1 and 2 years, the prevalence was low (~3%) but gradually increased so by 26 years it had reached 42%.[2-4,7,16,18-20]

Atopic dermatitis. Atopic dermatitis, using modified Hannifin and Rajka definition was approximately 10% during early childhood.[2-4,7,21]

Peanut allergy. We were among the first to describe the prevalence of peanut allergy in 4 year old children in the IOWBC.[22] More recently we described the natural history of peanut allergy over the first 18 years of life.[23] Subsequently, the prevalence rates in the IOWBC was compared with another cohort of children of the same age, born a few years later on the IOW and assessed for peanut allergy. This showed that sensitisation increased 3-fold and clinical allergy to peanut doubled during the 1990s.[24] In early 2000, we recruited another birth cohort on the IOW (Food Allergy and

Intolerance Research cohort) and assessed children for food allergy during early childhood. Therefore, we were able to compare prevalence in these 3 sequential cohorts of children, all aged 3-4 years but born 5-6 years apart. We found that after the initial rise in 1990s, the peanut prevalence in the UK stabilized during the last decade.[25]

Allergic sensitisation. The relationship of allergic sensitisation, asthma, and allergic disease was investigated from the ages of 4 to 26 years.[4,12,26-28] Atopy (SPT positive to any allergen) was 29% at 4 years.[4] A strong relationship was found between allergic diseases such as asthma with house dust mite, allergic rhinitis with grass pollen and eczema with egg.[7] Various childhood atopic phenotypes were described and their relationships with wheeze and asthma were defined. The population-attributable risk of atopy for asthma was 44%, for rhinitis it was 46% and for eczema, 32%.[2]

We recently showed that fractional exhaled nitric oxide (FeNO) is associated with atopy and atopic asthma, but not with non-atopic asthma. This has implications in the use of FeNO for the diagnosis and management of asthma.[27]

Natural history

Overall, the prevalence of wheeze and asthma has continued to rise from early childhood to early adult life. However, there was fluidity such that a proportion of children who had wheeze at one follow-up were not wheezing at the next, but other non-wheezing children had acquired wheeze so that the trend of period prevalence remained upwards. The remission, relapse, and new onset (in those who were previously disease free) was also seen in other allergic manifestations including eczema, rhinitis, food allergy and allergic sensitisation.[20,23,29-32] However, the net trend for asthma and rhinitis was generally upwards, for eczema and food allergy there was a relatively high prevalence in early childhood followed by overall stable figures of around 10-15% for eczema and 1-3% for food allergy.

We were among the first to report that children with egg allergy in infancy have a 5 to 6-fold increased risk of acquiring aeroallergen sensitisation and respiratory symptoms by age 4,[33] thus shifting the allergic phenotype from food allergy to aeroallergen sensitisation with associated asthma and rhinitis.

Risk factors for allergic diseases

Sex: Boys suffered from asthma, eczema, rhinitis and atopy (allergic sensitisation) more than girls throughout childhood and early adult life (up to age 26 years). For asthma, a gender reversal occurs during adolescence; thus at age 18 girls had more asthma than boys.[2,4,6-8,20,21,31,34]

Parental allergy. As expected, parental asthma and allergy had a consistent effect on childhood asthma and eczema over the entire childhood and adolescent period[2,3,6,7,18,21,34-36] with some disease specificity such that parental asthma increased the risk of asthma more than eczema or rhinitis .[4] We also showed that the risk is sex specific, such that boys had higher risk of asthma when their fathers were affected by asthma, while girls had a higher risk when mothers were diagnosed with asthma.[35]

Breastfeeding and asthma. The effect of breastfeeding on asthma remains controversial. We showed that breast feeding for at least 3 months protects against early childhood wheezing, [3,7] possibly as a result of attenuating the adverse effect of respiratory infections and maternal smoking on asthma.[37-39] We also showed that breastfeeding is associated with better lung function at 10 and 18 years of age.[38,40] However, the effect on allergic diseases in later childhood and adolescence was less clear.[41] Our data suggest that some of the conflicting results on method of feeding and allergy may be due to reverse causation.[42]

Low birth weight: Low birth weight was shown to be a risk factor for asthma, atopy and lung function.[34,36,39,43-45]

Exposure to smoking: We demonstrated the adverse effects of maternal smoking exposure on the developing foetus with increased risk of wheeze and nasal symptoms during infancy,[2,7,18,34,46] and of active smoking on lung health during adolescence.[6,15] Maternal smoking also had an effect on eczema at age 4 years.[46] The genetic susceptibility and epigenetic mechanisms mediating this susceptibility have been studied (see below). These findings have paved the way to identify susceptible smokers at risk of future COPD.

Lower socio-economic group: Children among the lower socioeconomic group had a higher level of infant wheezing even after adjusting for confounding factors such as lack of breast feeding and maternal smoking. [2,3,7]

Presence of pets: We have not found an effect of exposure to furry pets on asthma or other allergic diseases at any age.[2,3,18,21,34,47] A similar conclusion was reached in a meta-analysis of data from various European birth cohorts including the Isle of Wight.[48]

Season of birth: We have found effect of season of birth with a higher level of asthma and rhinitis during the summer.[2,3,7,49] Autumn births were associated with rhinitis and autumn and winter combined had more eczema.

Cord and maternal IgE: The presence of cord IgE was associated with maternal IgE[36] and increased the risk of allergic sensitisation at 4 years.[3] We also showed that IgE at birth (cord IgE) decreases with increasing birth order.[50] This provides an alternative explanation to the hygiene hypothesis for the lower incidence of allergic disease observed in younger siblings, as it seems they are born with lower cord IgE. We subsequently showed that this effect on children may be transmitted from the mother as their IgE also decreases with the increasing number of children they delivered.[51] We demonstrated that the birth order effect is dependent on genetic susceptibility. An interaction between an *IL13* gene polymorphism (rs20541) and birth order was found, whereby the effect of this SNP on skin test (ages 4 to 18), total IgE (age 10), and inhalant screen (age 10) was restricted to first-born children.[52]

Predictors

Using longitudinal and repeated assessments of allergic disease in our birth cohort and available information on risk factors and biomarkers, we attempted to identify predictive markers for asthma and allergy.[13,33,53,54] We initially focused on cord blood IgE and found that an elevated cord IgE increases the risk of allergic sensitisation during childhood.[53,55] Although it did not increase the risk of respiratory symptoms in early childhood, it did increase the risk of asthma at age 10.[55] However, the sensitivity of cord IgE was too low to be used as a predictive marker for allergic disease.[53,54] Another important issue in paediatric allergy is the outcome of infant wheeze and its relationship with later childhood asthma. We developed predictive scores, based on a set of 4 risk factors (maternal asthma, allergic sensitisation, recurrent chest infections, and absence of nasal symptoms). Among children with a risk score of 4, 83% persisted with their wheeze, while those with a risk score of zero, 80% went into remission.[13] Egg allergy combined with eczema during infancy had a high (>80%) positive predictive value for allergic sensitisation and respiratory symptoms.[33]

Genetics

We identified a novel gene (*ATPAF1*) association with childhood asthma using a genome-wide approach on pooled DNA.[56] Cohort data were also utilized to identify a novel gene regulating neutrophil function, which is responsible for severity in cystic fibrosis.[57] Using a candidate gene approach, we investigated the association of *IL13* with cord IgE and atopic eczema.[58,59] We have also demonstrated that filaggrin loss of function mutations contribute to allergic comorbidity including food allergy.[60-63] Gene-gene interaction between *GATA3* and *STAT6* with *IL13* on rhinitis and eczema, respectively, was demonstrated.[64,65]

Exposure to tobacco smoke increases the risk of wheeze and lung function deficit. We have shown the interaction of pre- and postnatal smoking exposure with genetic polymorphisms in genes encoding IL-13, IL-1R antagonist and GSTM2-5 on development of asthma and lung function.[66-68]

Exposures related to birth order modified the effect of *IL13* polymorphism on allergic sensitisation while filaggrin loss of function mutations modified the effect of breast-feeding on eczema.[52,69]

Epigenetics

We have explored epigenetic mechanisms using genome-wide DNA methylation.[49,70-82] Common environmental exposures such as smoking alter epigenetic profile, which in turn is shown to be associated with the risk of allergic diseases (Table 5). Interestingly, tetanus vaccination between 10 and 18 years was related to differential methylation, which in turn reduced the risk of asthma at 18 years.[79] Using a two-stage model we showed that genetic variants in combination with living conditions, for instance use of oral contraceptive in girls, may change the DNA-methylation, which in turn modifies the genetic associations related to asthma.[82] The interaction of DNA methylation with genetic variants was demonstrated for a number of allergic markers and diseases.[70-73,77]

What are the main strengths and weaknesses?

Strengths: The IOWBC is an unselected whole population cohort that truly represents the community from which the cohort is drawn. There has been a high retention rate of over 70% throughout, with availability of information and samples from the parental generation, comprehensive assessment that covered not only asthma but all chronic allergic conditions, prospective and extensive phenotyping, as well as genome-wide (epi)genotyping.

Weaknesses: Despite reletively high retention, some self-selection was observed in chidren who attended at avrious assessments (Table 2). For instacne, at 18 and 26 years, girls attended more than boys and children who were assessed tended to have a lower proportion of parental smoking and low (<2.5kg) birth weight. However, as the follow-up rates were consistently high (80-90%) and imbalances were few, this reletively modest selection bias does not affect the validity or generalisability of the findings. The Isle of Wight is a relatively small island (~20 miles across) and

therefore there is a lack of diversity, both in terms of environment (no industrial exposure) and race (>90% Caucasian), hence raising potential questions regarding generalisability of findings. The population is, however, not genetically inbred and there is frequent movement of people from mainland England.

Can I get hold of the data? Where can I find out more?

The cohort profile is available on www.allergyresearch.org.uk. We encourage collaboration to maximise the use of data and samples. We are in the process of finalising details of how the data can be accessed and the process of submitting an application to access the data. Please contact Mr. Stephen Potter (stephen.potter@iow.nhs.uk).

Profile in a nutshell –

Profile in a nutshell

- IOWBC is a whole population prospective, observational study investigating prevalence, natural history and risk and protective factors for the development of asthma and allergic diseases.
- All children (n=1536) born on the Isle of Wight between 1st January 1989 and 28th February 1990 were enrolled with 1456 consenting for long term follow-up.
- Participants have been assessed 6 times since birth with a high (>70%) retention of the cohort participants.
- A wide range of phenotypic and environmental information has been collected using questionnaires and hospital medical records, study procedures, genetic and epigenetic assessments and over 10,000 biological samples have been collected.

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Table 1. Information and samples collected from the Isle of Wight birth cohort

Variable	Birth	Year 1	Year 2	Year 4	Year 10	Year 18	Year 26
Family history of asthma, eczema, and rhinitis	x	x	x	x	x	x	x
Pregnancy complications and birth characteristics	x	-	-	-	-	-	-
Mode of feeding	-	x	x	-	-	-	-
Household pets	x	x	x	x	x	x	x
Socioeconomic status	x	x	x	x	x	x	x
Exposure to smoking	x	x	x	x	x	x	x
Height, weight, BMI	x	x	x	x	x	x	x
Housing characteristics	-	-	x	x	x	x	x
Wheeze and asthma	-	x	x	x	x	x	x
Nasal symptoms	-	x	x	x	x	x	x
Respiratory infections	-	x	x	x	x	x	x
Allergic symptoms	-	x	x	x	x	x	x
Eczema		x	x	x	x	x	x
Food allergy		x	x	x	x	x	x
Treatment and medications	-	x	x	x	x	x	x
Skin prick test	-	x	x	x	x	x	x
Total and specific IgE*	x	-	-	-	x	x	x
Spirometry and bronchodilator reversibility (FEV_1, FVC, FEF_{25-75})	-	-	-	-	x	x	x
Bronchial provocation test (PC_{20} and methacholine and dose-response)	-	-	-	-	x	x	x

Exhaled nitric oxide	-	-	-	-	-	x	x
Urinary cotinine	-	-	-	-	x	x	x
Genome-wide genotyping	-	-	-	-	x	-	-
Genome-wide DNA-methylation#	x	-	-	-	x	x	-
*Using maternal and cord blood #Using Guthrie cards collected at day 7							

Table 2. Comparison of participants who attended or did not attend at various assessments with regards to cohort characteristics and other information collected at birth.

	1 year		2 year		4 year		10 year		18 year		26 years	
	Attended (n=1369)[$]	**Not attended (n=167)**	**Attended (n=1231)**	**Not attended (n=305)**	**Attended (n=1218)**	**Not attended (n=318)**	**Attended (n=1373)**	**Not attended (n=163)**	**Attended (n=1313)**	**Not attended (n=213)**	**Attended (n=1033)**	**Not attended (n=503)**
Male gender	697/1369 (50.9%)	90/167 (53.9%)	622/1231 (50.5%)	165/305 (54.1%)	621/1218 (51.0%)	166/318 (52.2%)	698/1373 (50.8%)	89/163 (54.6%)	654/1313 (49.8%)*	133/223 (59.6%)	473/1033 (45.8%)*	314/503 (62.4%)
Low birth weight (<2.5Kg)	52/1347 (3.9%)*	14/165 (8.5%)	42/1210 (3.5%)	24/302 (7.9%)	45/1198 (3.8%)*	21/314 (6.7%)	53/1351 (3.9%)*	13/161 (8.1%)	48/1294 (3.7%)*	18/218 (8.3%)	40/1019 (3.9%)	26/493 (5.3%)
Maternal asthma	150/1362 (11.2%)	15/155 (9.7%)	129/1228 (10.5%)	36/289 (12.5%)	126/1211 (10.4%)	39/306 (12.7%)	143/1364 (10.5%)	22/153 (14.4%)	138/1304 (10.6%)	27/213 (12.7%)	112/1025 (10.9%)	53/492 (10.8%)
Paternal asthma	134/1354 (9.9%)	15/150 (10.0%)	115/1222 (9.4%)	34/282 (12.1%)	117/1208 (9.7%)	32/296 (10.8%)	131/1356 (9.7%)	18/148 (12.2%)	128/1296 (9.9%)	21/208 (10.1%)	98/1019 (9.6%)	51/485 (10.5%)
Sibling asthma	93/805 (11.6%)	13/79 (16.5%)	78/722 (10.8%)*	28/162 (17.3%)	73/712 (10.3%)*	33/172 (19.2%)	88/800 (11.0%)*	18/84 (21.4%)	88/756 (11.6%)	18/128 (14.1%)	70/602 (11.6%)	36/282 (12.8%)
Maternal eczema	166/1359 (12.2%)	17/155 (11.0%)	150/1225 (12.2%)	33/289 (11.4%)	145/1208 (12.0%)	38/306 (12.4%)	162/1361 (11.9%)	21/153 (13.7%)	161/1301 (12.4%)	22/213 (10.3%)	125/1023 (12.2%)	58/491 (11.8%)
Paternal eczema	86/1352 (6.4%)	11/152 (7.2%)	80/1220 (6.6%)	17/284 (6.0%)	78/1206 (6.5%)	19/298 (6.4%)	89/1355 (6.6%)	8/149 (5.4%)	90/1294 (7.0%)*	7/210 (3.3%)	74/1017 (7.3%)	23/487 (4.7%)
Sibling eczema	192/801 (24.0%)	14/79 (17.7%)	168/718 (23.4%)	38/162 (23.5%)	167/708 (23.6)	39/172 (22.7%)	195/796 (24.5%)	11/84 (13.1%)	181/752 (24.1%)	25/128 (19.5%)	136/599 (22.7%)	70/281 (24.9%)
Maternal rhinitis	278/1362 (20.4%)	27/155 (17.4%)	246/1228 (20.0%)	59/289 (20.4%)	257/1211 (21.2%)*	48/306 (15.7%)	270/1364 (19.8%)	35/153 (22.9%)	262/1304 (20.1%)	43/213 (20.2%)	210/1025 (20.5%)	95/492 (19.3%)
Paternal rhinitis	202/1353 (14.9%)	18/152 (11.8%)	179/1222 (14.6%)	41/283 (14.5%)	177/1207 (14.7%)	43/298 (14.4%)	201/1356 (14.8%)	19/149 (12.8%)	189/1296 (14.6%)	31/209 (14.8%)	151/1018 (14.8%)	69/487 (14.2%)
Sibling rhinitis	58/801 (7.2%)	3/79 (3.8%)	50/719 (7.0%)	11/161 (6.8%)	50/708 (7.1%)	11/172 (6.4%)	55/796 (6.9%)	6/84 (7.1%)	55/752 (7.3%)	6/128 (4.7%)	38/599 (6.3%)	23/281 (8.2%)
Maternal smoking	345/1354 (25.5%)	48/155 (31.0%)	295/1221 (24.2%)*	98/288 (34.0%)	257/1206 (21.3%)*	136/303 (44.9%)	325/1357 (23.9%)*	68/152 (44.7%)	311/1298 (24.0%)*	82/211 (38.9%)	233/1020 (22.8%)*	160/489 (32.7%)
Paternal smoking	539/1353 (39.8%)	69/150 (46.0%)	476/1221 (39.0%)*	132/282 (46.8%)	437/1207 (36.2%)*	171/296 (57.8%)	523/1355 (38.6%)*	85/148 (57.4%)	503/1296 (38.8%)*	105/207 (50.7%)	384/1018 (37.7%)*	224/485 (46.2%)
Cat ownership	452/1361 (33.2%)	42/153 (27.5%)	411/1227 (33.5%)	83/287 (28.9%)	403/1211 (33.3%)	91/303 (30.0%)	454/1364 (33.3%)	40/150 (26.7%)	434/1303 (33.3%)	60/211 (28.4%)	340/1023 (33.2%)	154/491 (31.4%)

Dog ownership	403/1361 (29.6%)	38/153 (24.8%)	363/1227 (29.6%)	78/287 (27.2%)	356/1211 (29.4%)	85/303 (28.1%)	396/1364 (29.0%)	45/150 (30.0%)	376/1303 (28.9%)	65/211 (30.8%)	293/1023 (28.6%)	148/491 (30.1%)
Social class I–III	441/799 (55.2%)	45/91 (49.5%)	319/715 (44.6%)	85/175 (48.6%)	347/721 (48.1%)	57/169 (33.7%)	376/811 (46.4%)	28/79 (35.4%)	357/779 (45.8%)	47/111 (42.3%)	292/601 (48.6%)*	112/289 (38.8%)
Cord IgE > 0.5	129/1000 (12.9%)	10/64 (15.6%)	118/928 (12.7%)	21/136 (15.4%)	139/1064 (13.1%)	0/152 (0%)*	130/1016 (12.8%)	9/48 (18.8%)	122/973 (12.5%)	17/91 (18.7%)	96/756 (12.7%)	43/308 (14.0%)

Note: $: Attended n= denotes maximum number of children who provided any information at a given assessment. There were some missing information depending on the specific question with the details provided for each in the rows below.

*where differences were found to be statistically significant between those who attended and did not attend defind as $p<0.05$

Table 3. Procedures conducted in the Isle of Wight cohort (n)

Variable	Birth	Year 1	Year 2	Year 4	Year 10	Year 18	Year 26
Questionnaires	1536	1,369	1,231	1,218	1,373	1,313	1033
Physical examination	-	323	410	977	1036	864	544
Height/weight	1501	1090	399	1053	1043	964	681
Skin prick tests	-	323	410	977	1036	851	556
Spirometry	-	-	-	-	980	839	544
Bronchialprovocation tests	-	-	-	-	784	586	ongoing
Sputum induction	-	-	-	-	25	100	-
Exhaled nitric oxide	-	-	-	-	-	822	542
Blood samples	Maternal=1150 Cord=1275 Guthrie card at 7 day= 1150	-	-	-	950	550	503
Urine	-	-	-	-	970	650	528
Saliva	-	-	-	-	850	500	22

Table 4. Demographic characteristics of the parents of the Isle of Wight Birth Cohort particiants (recorded at recruitment)

	Mothers	**Fathers**
Mean age (years)	27.25	-
Smoking (n)	393	608
Cat ownership (n)	494	-
Dog ownership (n)	442	-
Asthma (n)	165	149
Hay fever (n)	305	220
Eczema (n)	183	97
Food allergy (n)	71	38
Any allergic disease (n)	528	388

Table 5. Epigenetics associations identified in the Isle of Wight Birth Cohort participants

Main CpG site/s	Genes	Exposure	Outcomes	Reference
cg09791102 cg26937798	*IL-4* *IL-4*	-	on asthma risk and temporal asthma transition	Zhang et al. Clin Epigenetics. 2014 Apr 15;6(1):8.
cg07548383	*FLG*	-	eczema,	Ziyab J Eur Acad Dermatol Venereol 2012;7(3):e32721
cg09791102	*IL-4R*	-	asthma at age 18 years	Soto-Ramirez et al, Clinical Epigenetics 2013 Jan 3;5(1):1),
cg00666422	*LEP*	-	lung function and asthma	Mukherjee Int J Mol Epidemiol Genet. 2016 Mar 23;7(1):1-17
cg04850479 cg01427769	*PROZ* *NEU1*	-	Eczema	Quraishi et al. Clin Epigenetics. 2015 Jul 21;7(1):68.
cg04983687 cg18219873 cg27469152 cg09332506	*ZFPM1* *PRG2* *EPX* *COPA*	-	atopy and high serum IgE	Everson T Genome Med. 2015 Aug 21;7(1):89.
cg11807188 cg03050981	*LEPR/LEPROT*	Smoking	Serum pleptin/BMI	Yousefi et al. Int J Mol Epidemiol Genet. 2013 Jun;4(2):86-100
cg13566430	*IL-13*	Smoking	asthma	Patil et al. Clin Epigenetics. 2013 Dec;5(1):22.
cg00787537 cg24577417 cg07175945	*KCNH1* *HGC6.3* *ZFR*	Season of Birth	allergic Disease	Lockett GA Allergy. 2016 Mar 12. doi: 10.1111/all.12882.
cg05575921	*AHRR*	Maternal Smoking	-	Joubert Am J Hum Genet 2016 Apr 7;98(4):680-96
Cg14472551 cg01669161	*KIAA1549L* *PSMG3, TFAMP1*	Tetanus vaccination	asthma	Janjanam et al. Vaccine. 2016 Dec 12;34(51):6493-6501
CpG islands	*NHP2L1, WRB and PPIEL*	-	-	Docherty et al. J Med Genet. 2014 Apr;51(4):229-38

Figure 1: Flow diagram of study progress