Supporting information

**Systematic review on the definition of allergic diseases in children: The MeDALL study**

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# Table S1. Objectives of the systematic review

|  |  |
| --- | --- |
| Primary objective | To identify clinically expressed, population-based, phenotypes of IgE-associated diseases or conditions including asthma/wheezing, atopic eczema, rhinoconjuctivitis, food allergy, urticaria and anaphylaxis, as well as their interrelationships, from childhood to young adulthood. |
| Secondary objective (1) | To explore heterogeneity within phenotypes.  By heterogeneitywemean that subjects classified into a specific phenotype (such as asthma) can show intra-phenotype differences that can be better organised by re-classification of the phenotype in two or more groups (Transient or Persistent wheezers). |
| Secondary objective (2) | To appraise the varied approaches to measure phenotypes.  Approaches refer both to study design and type of measures where several data can be used: IgE levels (chord blood and follow-up serum), skin allergy testing such as SPT, pulmonary-function testing, co-morbidities, questionnaires etc. Depending on the data used, distinct phenotypes can be defined. For example, some studies assess the presence of a new phenotype in longitudinal studies looking at the course of the disease whereas other studies look at cross-sectional associations with disease markers. |

# Table S2. Characteristics of the included studies

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ref.** | **Country** | **year** | **Nº citup to 2012** | **Nº citin 2013** | **Study design** | **Recruit period** | **Study pop** | **Sample size** | **Disease conditions** | **Disease conditions in title** |
| **Hall et al**[1] | Australia | 1972 | 0 | 0 | CS | 1968 | P | 8410 | NS | A;R;E |
| **Mcnicol et al**[2] | Australia | 1973 | 243 | 0 | Cohort | 1965-1975 | P | 397 | A | A |
| **Giles et al**[3] | Australia | 1984 | 30 | 2 | Cohort | 1968-1981 | P | 851 | NS | A;R;E |
| **Peat et al**[4] | Australia | 1989 | 89 | 1 | Cohort | 1982-1986 | P | 380 | NS | A |
| **Van Asperen and Kemp**[5] | Australia | 1989 | 55 | 1 | Cohort |  | C | 57 | NS | A;FA;R;E |
| **Peat et al**[6] | Australia | 1990 | 195 | 2 | Cohort | 1982-1986 | P | 380 | NS | A;R;E |
| **Van Asperen et al**[7] | Australia | 1990 | 31 | 0 | Cohort |  | P | 52 | NS | A;R;E |
| **Peat and Woolcock**[8] | Australia | 1991 | 117 | 1 | CS | 1982-1986 | P | 3581 | NS | A;R;E |
| **Toelle et al**[9] | Australia | 1992 | 218 | 2 | CS | 1988-1990 | P | 352 | A | A |
| **Peat et al** [10] | Australia | 1993 | 46 | 1 | Cohort | 1988-1989 | P | 236 | NS | A |
| **Van Asperen and Mukhi**[11] | Australia | 1994 | 31 | 0 | Cohort |  | P | 47 | A | A |
| **Toelle et al** [12] | Australia | 1997 | 9 | 0 | Cohort | 1982-1992 | P | 407 | A | A |
| **Young et al**[13] | Australia | 2000 | 91 | 3 | Cohort | 1987-1991 | P | 160 | A | A |
| **Palmer et al**[14] | Australia | 2001 | 102 | 3 | Cohort | 1987-1991 | C | 120 | A | A |
| **Gibson et al**[15] | Australia | 2001 | 35 | 0 | CS |  | P | 83 | A | A |
| **Ponsonby et al**[16] | Australia | 2002 | 38 | 1 | CS | 1999 | P | 758 | A | A |
| **Kusel et al.**[17] | Australia | 2007 | 192 | 24 | Cohort |  | P | 198 | A | A |
| **Almqvist et al**[18] | Australia | 2007 | 38 | 1 | Cohort | 1997-2004 | P | 375 | A;NS | A;R;E |
| **Lowe et al**[19] | Australia | 2007 | 35 | 3 | Cohort | 1990-1994 | P | 443 | A;R;E | A;R;E |
| **Hollams et al**[20] | Australia | 2009 | 24 | 2 | CS |  | P | 1380 | A | A;R |
| **Schultz et al**[21] | Australia | 2010 | 29 | 5 | Clinical trial |  | C | 109 | A | A |
| **Holt et al**[22] | Australia | 2010 | 27 | 6 | Cohort |  | P | 198 | A | A |
| **Wang et al**[23] | Australia | 2011 | 12 | 7 | CC |  | C | 86 | A | A |
| **Govaere et al**[24] | Belgium | 2009 | 5 | 1 | CS | 2004-2005 | P | 2021 | NS | A;R;E |
| **Lopez et al**[25] | Brazil | 2002 | 11 | 0 | Cohort | 1996-1997 | C | 102 | A | A |
| **Solé et al**[26] | Brazil | 2005 | 32 | 0 | CS | 1999 | P | 6490 | A;R;E | A;R;E |
| **Pereira et al**[27] | Brazil | 2007 | 43 | 1 | CS |  | P | 1982 | A | A |
| **Baehler et al**[28] | Canada | 1996 | 33 | 1 | Case series | 1993-1994 | C | 69 | FA | A;FA;R;U;E;Ana |
| **Lawson et al**[29] | Canada | 2007 | 4 | 0 | Cohort | 2000-2003 | P | 212 | A | A |
| **Castro-Rodriguez et al**[30] | Chile | 2007 | 14 | 0 | CS |  | C | 237 | A | A |
| **Hon et al**[31] | China | 2008 | 16 | 1 | CC | 2008 | C | 105 | E | FA;U;E |
| **Celedón et al**[32] | Costa Rica | 2002 | 13 | 1 | CC | 1998-1999 | P | 198 | A;R;E | A;R;E |
| **Bunyavanich et al**[33] | Costa Rica | 2010 | 6 | 1 | CS | 2001-2006 | P | 616 | A;R | A;R |
| **BraaeOlesen et al**[34] | Denmark | 2001 | 0 | 0 | CS | 1999-2000 | P | 61 | E | E |
| **Johnke et al**[35] | Denmark | 2005 | 30 | 1 | Cohort |  | P | 562 | E | E |
| **Bisgaard et al**[36] | Denmark | 2006 | 219 | 13 | Clinical trial | 1998-2001 | P | 294 | A | A |
| **Halkjaer et al**[37] | Denmark | 2006 | 36 | 3 | Cohort | 1998-2004 | P | 356 | E | E |
| **Johnke et al**[38] | Denmark | 2006 | 28 | 3 | Cohort |  | P | 562 | E | E |
| **Eller et al**[39] | Denmark | 2009 | 17 | 3 | Cohort | 1998-1999 | P | 562 | FA | FA;E |
| **Chawes et al**[40] | Denmark | 2009 | 18 | 2 | Cohort |  | P | 255 | R | R |
| **Kjaer et al**[41] | Denmark | 2009 | 14 | 9 | Cohort | 1998-2005 | P | 404 | NS | A;FA;R;E |
| **Chawes et al**[42] | Denmark | 2010 | 14 | 6 | Cohort |  | C | 290 | A;R | A;R;E |
| **Hyvärinen et al**[43] | Finalnd | 2005 | 24 | 0 | Cohort | 1981-1995 | C | 98 | A | A;R;E |
| **Luoma et al**[44] | Finland | 1983 | 45 | 0 | Cohort | 1971-1978 | P | 543 | A;R;E | A;R;E |
| **Kekki et al**[45] | Finland | 1997 | 46 | 2 | Clinical trial |  | C | 113 | E | FA;E |
| **Tikkanen et al**[46] | Finland | 2000 | 23 | 0 | Cohort | 1986-1997 | C | 260 | FA | A;FA;R;E |
| **Reijonen et al**[47] | Finland | 2000 | 76 | 1 | Clinical trial | 1992-1997 | C | 89 | A | A |
| **Kotaniemi-Syrjänen et al**[48] | Finland | 2002 | 32 | 1 | Cohort | 1992-1999 | C | 82 | A | A;FA;R;E |
| **Hyvärinen et al**[49] | Finland | 2005 | 39 | 7 | Cohort | 1992-2004 | C | 81 | A | A |
| **Saarinen et al**[50] | Finland | 2005 | 106 | 14 | CC | 2003-2004 | P | 118 | FA | A;FA;R;U;E |
| **Jartti et al**[51] | Finland | 2009 | 20 | 6 | CS | 2000-2002 | C | 259 | A | A;FA;E |
| **Delacourt et al**[52] | France | 1994 | 65 | 1 | Cohort | 1990-1993 | C | 67 | A | A |
| **Mortureux et al**[53] | France | 1998 | 66 | 3 | Cohort | 1992-1994 | C | 40 | U | U |
| **Tridon et al**[54] | France | 1999 | 4 | 0 | Case series |  | C | 44 | A | A |
| **Pénard-Morand et al**[55] | France | 2005 | 47 | 2 | CS | 1999-2000 | P | 6672 | A;FA;R | A;FA;R |
| **Herr et al**[56] | France | 2011 | 5 | 6 | Cohort | 2003-2004 | P | 1850 | R | A;R;E |
| **Bergmann et al**[57] | Germany | 1998 | 142 | 3 | Cohort | 1990-1995 | P | 1004 | A;NS | A;R;E |
| **Schäfer et al**[58] | Germany | 1999 | 107 | 4 | CC | 1992-1993 | P | 2201 | E | E |
| **Kulig et al**[59] | Germany | 2000 | 74 | 3 | Cohort | 1990 | P | 587 | R | A;FA;R;E |
| **Illi et al**[60] | Germany | 2001 | 163 | 4 | Cohort | 1990 | P | 939 | A | A |
| **Riedinger et al**[61] | Germany | 2002 | 8 | 0 | Cohort | 1996-1999 | P | 1101 | A;R | A;R |
| **Lau et al**[62] | Germany | 2003 | 32 | 1 | Cohort | 1990-1997 | P | 939 | A | A |
| **Fritz and Herbarth**[63] | Germany | 2004 | 6 | 1 | CS | 1993-1994 | P | 734 | A | A;R;E |
| **Laske and Niggeman**[64] | Germany | 2004 | 40 | 1 | CS |  | C | 345 | E | E |
| **Illi et al**[65] | Germany | 2004 | 246 | 28 | Cohort | 1990 | P | 1123 | A;E | A;E |
| **Niggemann et al**[66] | Germany | 2004 | 19 | 0 | Case series |  | C | 74 | FA;E | FA;E |
| **Illi et al**[67] | Germany | 2006 | 56 | 31 | Cohort | 1990 | P | 1314 | A | A |
| **Brockow et al**[68] | Germany | 2009 | 18 | 4 | Cohort | 1995-1998 | P | 1290 | NS | A;R;E |
| **Schnabel et al**[69] | Germany | 2010 | 13 | 3 | Cohort | 1997-1999 | P | 1082 | FA | FA |
| **Peters et al**[70] | Germany | 2010 | 10 | 4 | Cohort | 1995-2003 | P | 2857 | E | E |
| **Rochat et al**[71] | Germany | 2010 | 18 | 5 | Cohort | 1990 | P | 766 | A;R | A;R |
| **Priftis et al**[72] | Greece | 2008 | 11 | 1 | CC | 1995-1998 | C | 223 | A | A |
| **Hidvegi et al**[73] | Hungary | 2002 | 18 | 1 | Case series |  | C | 80 | FA | FA |
| **Pourpak et al**[74] | Iran | 2007 | 0 | 1 | Case series | 2001-2004 | C | 19 | Ana | FA;Ana |
| **Geller-Bernstein et al**[75] | Israel | 1987 | 22 | 0 | Cohort |  | C | 80 | A | A |
| **Roizin et al**[76] | Israel | 1996 | 4 | 0 | Case series |  | C | 39 | A | A |
| **Novembre et al**[77] | Italy | 1998 | 84 | 8 | Case series | 1994-1996 | C | 76 | Ana | Ana |
| **Patrizi et al**[78] | Italy | 2000 | 18 | 1 | Cohort |  | C | 78 | E | A;E |
| **Pajno et al**[79] | Italy | 2003 | 17 | 1 | Cohort |  | C | 71 | E | E |
| **Peroni et al**[80] | Italy | 2003 | 48 | 4 | CS | 2000-2001 | P | 1121 | R | A;R;E |
| **Fasce et al**[81] | Italy | 2004 | 27 | 2 | Cohort |  | C | 340 | A | A |
| **Fiocchi et al**[82] | Italy | 2004 | 17 | 0 | CS | 2000-2001 | C | 147 | A;E | A;E |
| **Cantani and Micera**[83] | Italy | 2004 | 13 | 1 | Cohort |  | C | 115 | FA | A;FA;R;E |
| **Cardinale et al**[84] | Italy | 2005 | 5 | 0 | CC | 2002-2003 | C | 175 | A;R | A;R |
| **De Sario et al**[85] | Italy | 2006 | 15 | 2 | CS | 2000-2001 | P | 1717 | A | A |
| **Barberio et al**[86] | Italy | 2008 | 10 | 1 | Cohort | 1993-1997 | C | 692 | NS | A;R;E |
| **Jesenak et al**[87] | Italy | 2008 | 3 | 0 | CS | 2005-2006 | P | 532 | NS | A;FA;R |
| **Ciprandi and Capasso**[88] | Italy | 2010 | 5 | 3 | CS |  | C | 200 | R | A;R |
| **Cibella et al**[89] | Italy | 2011 | 2 | 2 | CS | 2005-2006 | P | 2150 | NS | A;R;E |
| **Toyoshima et al**[90] | Japan | 1987 | 3 | 0 | Cohort |  | C | 48 | A | A |
| **Rokaite and Labanauskas**[91] | Lithuania | 2005 | 5 | 0 | CS |  | C | 164 | E | FA;E |
| **Crane et al**[92] | New Zealand | 1989 | 24 | 0 | CS | 1984 | P | 494 | A | A |
| **Nystad et al**[93] | Norway | 1998 | 20 | 0 | CS | 1994 | P | 502 | NS | A |
| **LodrupCarlsen et al**[94] | Norway | 1999 | 24 | 0 | CC | 1992-1994 | P | 165 | A | A |
| **Smidesang et al**[95] | Norway | 2010 | 2 | 0 | Cohort | 2000 | P | 4783 | NS | A;FA;R;E |
| **Bertelsen et al**[96] | Norway | 2010 | 7 | 4 | Cohort | 1992-2002 | P | 1015 | R | A;R;E;Ana |
| **Lang et al**[97] | Norway | 2010 | 11 | 3 | CS | 2006-2007 | C | 115 | A | A;R;E |
| **Jedrychowski et al**[98] | Poland | 2009 | 10 | 2 | Cohort | 2000-2004 | P | 468 | A | A |
| **Czarnobliska et al**[99] | Poland | 2011 | 7 | 0 | CS |  | P | 143 | E | E |
| **Kidon et al**[100] | Singapore | 2011 | 0 | 0 | Case series | 2004-2007 | C | 253 | NS | A;R;E |
| **Chiang et al**[101] | Singapore | 2012 | 1 | 0 | CS | 2001-2009 | C | 6660 | R | A;FA;R;E |
| **Mercer et al**[102] | South Africa | 2002 | 9 | 1 | CS | 1984-1993 | C | 771 | R | A;FA;R;U;E |
| **Lee et al**[103] | South Korea | 2013 | 0 | 0 | CS | 2006-2009 | C | 247 | A | A |
| **Oh et al**[104] | South Korea | 2013 | 0 | 0 | CS | 2010 | P | 372 | A | A |
| **Villa et al**[105] | Spain | 1998 | 25 | 0 | Cohort | 1993-1995 | C | 38 | A | A;FA;E |
| **Martín-Muñoz et al**[106] | Spain | 2008 | 4 | 0 | CS |  | C | 82 | A | A;FA;R;E |
| **Garcia-Marcos et al**[107] | Spain | 2010 | 4 | 0 | CS |  | P | 736 | A;R | A;R |
| **Foucard and Sjöberg**[108] | Sweden | 1984 | 78 | 2 | Cohort | 1968-1970 | C | 80 | A | A |
| **Rylander et al**[109] | Sweden | 1988 | 17 | 0 | Cohort | 1980-1984 | C | 67 | A | A |
| **Croner and Kjellman**[110] | Sweden | 1992 | 99 | 1 | Cohort | 1974-1988 | P | 89 | A | A;R;E |
| **Hattevig et al**[111] | Sweden | 1993 | 152 | 4 | Cohort |  | P | 84 | NS | A;FA;R;U;E |
| **Wennergren et al**[112] | Sweden | 1997 | 67 | 1 | Cohort | 1984-1985 | C | 92 | A | A |
| **Rönmark et al**[113] | Sweden | 1999 | 84 | 5 | CS | 1996 | P | 3431 | A | A |
| **Gustafsson et al**[114] | Sweden | 2000 | 152 | 11 | Cohort |  | C | 94 | A;E | A;FA;R;U;E |
| **Böhme et al**[115] | Sweden | 2002 | 40 | 1 | Cohort | 1994-1996 | P | 3791 | E | A;FA;R;U;E |
| **Wickman et al**[116] | Sweden | 2003 | 38 | 1 | Cohort | 1994-1996 | P | 2614 | NS | A;R;E |
| **Gustafsson et al**[117] | Sweden | 2003 | 34 | 0 | Cohort |  | C | 94 | E | E |
| **Sandin et al**[118] | Sweden | 2004 | 29 | 3 | Cohort | 1996-1997 | P | 1228 | A | A |
| **Ostblom et al**[119] | Sweden | 2007 | 13 | 4 | Cohort | 1999-2000 | P | 2563 | FA | A;FA;R;U;E |
| **Ostblom et al**[120] | Sweden | 2008 | 23 | 4 | Cohort | 1994-1996 | P | 1857 | FA;NS | A;FA;R;E |
| **Arsanoj et al**[121] | Sweden | 2010 | 27 | 11 | CS | 2002-2004 | P | 200 | NS | FA |
| **Westman et al**[122] | Sweden | 2012 | 2 | 9 | Cohort | 1994-2002 | P | 2024 | R | A;FA;R;E |
| **Chang et al**[123] | Taiwan | 2013 | 0 | 0 | Case series | 2002-2006 | C | 165 | U | A;R;U;E |
| **Shen et al**[124] | Taiwan | 2013 | 0 | 1 | Cohort | 2000-2010 | P | 29372 | A;R;E | A;R;E |
| **Sanqsupawanich et al**[125] | Thailand | 2007 | 2 | 0 | Cohort | 2000-2002 | P | 4021 | A;E | A;E |
| **Montefort et al**[126] | The Maltese Islands | 2002 | 14 | 1 | CS |  | P | 3506 | NS | A;R;E |
| **Duiverman et al**[127] | The Netherlands | 1987 | 47 | 0 | CC |  | C | 77 | NS | A |
| **Laan et al**[128] | The Netherlands | 2000 | 30 | 1 | Cohort |  | P | 103 | NS | A;FA;R;E |
| **Brussee et al**[129] | The Netherlands | 2004 | 36 | 5 | CS |  | P | 838 | A | A |
| **Schönberger et al**[130] | The Netherlands | 2004 | 8 | 0 | Cohort | 1967-1989 | C | 1586 | A | A |
| **Brussee et al**[131] | The Netherlands | 2005 | 0 | 0 | Cohort |  | P | 429 | A | A |
| **Jacobs and Brand**[132] | The Netherlands | 2010 | 1 | 0 | Case series | 1990-2003 | C | 244 | NS | A;FA;R;U;E;Ana |
| **Gürkan et al**[133] | Turkey | 2002 | 5 | 0 | Case series | 1995-1997 | C | 61 | A | A |
| **Saraçlar et al**[134] | Turkey | 2003 | 0 | 0 | CS | 1999-2000 | P | 3041 | A | A |
| **Sackesen et al**[135] | Turkey | 2004 | 37 | 3 | CS | 2001-2002 | C | 54 | U | U |
| **Kuyucu et al**[136] | Turkey | 2006 | 25 | 2 | CS | 1999-2000 | P | 2774 | R | A;R;E |
| **Baris et al**[137] | Turkey | 2011 | 1 | 0 | Cohort |  | C | 78 | A | A |
| **Civelek et al**[138] | Turkey | 2011 | 7 | 3 | CS | 2006 | P | 6963 | A | A;R |
| **Yavuz et al**[139] | Turkey | 2011 | 1 | 3 | CS | 2002-2009 | C | 315 | FA | A;FA;R;E;Ana |
| **Keles et al**[140] | Turkey | 2012 | 0 | 0 | CC | 2007-2010 | C | 108 | A | A |
| **Price et al**[141] | UK | 1976 | 11 | 0 | CS | 1974 | C | 42 | E | A;E |
| **Blair et al**[142] | UK | 1977 | 244 | 0 | Cohort | 1948-1972 | C | 244 | A | A;R;E |
| **Gordon et al**[143] | UK | 1982 | 67 | 0 | Cohort |  | C | 250 | A;E | A;E |
| **Lee et al**[144] | UK | 1983 | 203 | 1 | CS | 1979 | P | 2700 | A | A |
| **Park et al**[145] | UK | 1986 | 75 | 0 | Cohort | 1970-1980 | P | 2345 | A | A |
| **Clifford et al**[146] | UK | 1989 | 75 | 1 | CS |  | P | 330 | NS | A |
| **Sporik et al**[147] | UK | 1991 | 167 | 2 | Cohort | 1977-1989 | C | 67 | A | A;R;E |
| **Salob et al**[148] | UK | 1993 | 24 | 0 | CS |  | P | 61 | E | A;E |
| **Wilson et al**[149] | UK | 1995 | 20 | 0 | Case series |  | C | 40 | NS | A |
| **Brooke et al**[150] | UK | 1995 | 88 | 0 | Cohort | 1990-1994 | P | 488 | NS | A |
| **Christie et al**[151] | UK | 1997 | 12 | 0 | CS |  | P | 133 | A | A |
| **Withers et al**[152] | UK | 1998 | 79 | 1 | Cohort | 1987 | P | 2289 | NS | A |
| **Christie et al**[153] | UK | 1999 | 22 | 0 | CS | 1989 | P | 95 | A | A |
| **Clough et al**[154] | UK | 1999 | 52 | 2 | Cohort | 1993-1996 | C | 107 | A | A |
| **McKenzie et al**[155] | UK | 2000 | 47 | 2 | CC |  | C | 203 | A | A |
| **Arshad et al**[156] | UK | 2001 | 154 | 14 | Cohort | 1989-1990 | P | 981 | NS | A;R;E |
| **Sherriff et al**[157] | UK | 2001 | 69 | 3 | Cohort | 1991-1992 | P | 8594 | A | A |
| **Arshad et al**[158] | UK | 2002 | 14 | 3 | Cohort | 1989-1990 | P | 1373 | R | A;FA;R;U;E |
| **Kurukulaaratchy et al**[159] | UK | 2003 | 75 | 9 | Cohort | 1989-1990 | P | 1034 | A | A;FA;E |
| **Kurukulaaratchy et al**[160] | UK | 2003 | 15 | 3 | Cohort | 1989-1990 | P | 1373 | E | A;FA;R;U;E |
| **Kurukulaaratchy et al**[161] | UK | 2003 | 58 | 6 | Cohort | 1989-1990 | P | 1034 | A | A |
| **Kurukulaaratchy et al**[162] | UK | 2004 | 58 | 4 | Cohort | 1989-1990 | P | 1034 | A | A |
| **Ben-Gashir et al**[163] | UK | 2004 | 15 | 1 | Cohort | 1998-1999 | P | 137 | E | E |
| **Perkin et al**[164] | UK | 2004 | 16 | 0 | Cohort | 1991-1992 | P | 2009 | E | E |
| **Kurukulaaratchy et al**[165] | UK | 2004 | 44 | 5 | Cohort | 1989-2000 | P | 1373 | A | A |
| **Lowe et al**[166] | UK | 2005 | 89 | 6 | Cohort |  | P | 874 | A | A |
| **Kurukulaaratchy et al**[167] | UK | 2005 | 51 | 4 | Cohort | 1989-1990 | P | 1456 | NS | A;FA;R;E |
| **Kurukulaaratchy et al**[168] | UK | 2005 | 19 | 3 | Cohort | 1989-2000 | P | 1034 | A | A |
| **Wassall et al**[169] | UK | 2005 | 6 | 1 | CS |  | P | 5998 | A | A |
| **Carroll et al**[170] | UK | 2006 | 23 | 7 | CS | 1999-2001 | C | 400 | A | A |
| **Kurukulaaratchy et al**[171] | UK | 2006 | 24 | 2 | Cohort | 1989-2000 | P | 1373 | A | A |
| **Marinho et al**[172] | UK | 2007 | 42 | 8 | Cohort |  | P | 815 | R | A;R;E |
| **Elphick et al**[173] | UK | 2007 | 10 | 0 | Cohort |  | C | 114 | A | A |
| **Sonnappa et al**[174] | UK | 2010 | 26 | 7 | CC |  | C | 134 | A | A |
| **Fleming et al**[175] | UK | 2012 | 1 | 13 | Cohort | 2005-2008 | C | 79 | A | A |
| **Halonen et al**[176] | USA | 1992 | 87 | 1 | Cohort | 1980-1984 | P | 767 | E;NS | A;E |
| **Martinez et al**[177] | USA | 1995 | 1874 | 87 | Cohort | 1980-1984 | P | 826 | A | A |
| **Stein et al**[178] | USA | 1997 | 159 | 2 | Cohort | 1980-1984 | P | 600 | A | A |
| **Chan et al**[179] | USA | 1998 | 102 | 10 | Case series | 1993-1997 | C | 164 | A | A |
| **Martinez et al**[180] | USA | 1998 | 84 | 1 | Cohort | 1980-1984 | P | 383 | A | A |
| **Sherrill et al**[181] | USA | 1999 | 71 | 0 | Cohort | 1980-1995 | C | 540 | A | A |
| **Halonen et al**[182] | USA | 1999 | 44 | 2 | Cohort | 1980-1984 | P | 741 | A | A |
| **Bansal et al**[183] | USA | 2001 | 4 | 1 | CS |  | C | 483 | A | A |
| **Klinnert et al**[184] | USA | 2001 | 81 | 4 | Cohort | 1985-1987 | P | 150 | A | A |
| **Kelley et al**[185] | USA | 2005 | 17 | 1 | CS | 1988-1994 | P | 5244 | A | A |
| **Morgan et al**[186] | USA | 2005 | 242 | 14 | Cohort |  | P | 826 | A | A |
| **Borish et al**[187] | USA | 2005 | 43 | 5 | CS | 2001 | C | 4756 | A | A |
| **Bacharier et al**[188] | USA | 2007 | 43 | 4 | Clinical trial | 2004 | C | 238 | A | A |
| **Schroeder et al**[189] | USA | 2009 | 31 | 3 | CS |  | C | 567 | A;FA | A;FA |
| **Wegienka et al**[190] | USA | 2009 | 2 | 0 | Cohort | 1987-1995 | P | 724 | A | A |
| **Keet et al**[191] | USA | 2009 | 23 | 5 | Cohort | 1993-2007 | C | 103 | FA | A;FA;R;E;Ana |
| **Wang et al**[192] | USA | 2010 | 33 | 11 | CC |  | C | 41 | FA | FA |
| **Fitzpatrick et al**[193] | USA | 2010 | 29 | 7 | CC |  | C | 53 | A | A |
| **Sala et al**[194] | USA | 2011 | 0 | 0 | CC | 2008-2009 | C | 188 | A | A |
| **Wolkerstorfer et al**[195] | International | 2002 | 40 | 3 | Clinical trial |  | C | 382 | E | FA;E |
| **Karadag et al**[196] | International | 2007 | 13 | 0 | CS | 2000-2002 | P | 14893 | A;E | A;R;E |
| **Pillai et al**[197] | International | 2008 | 13 | 1 | CS |  | P | 1563 | A | A |

CS: cross-sectional; CC: case-control; P: Population-based ; C: Clinical population; A: Asthma and/or wheeze; R: Rhinitis; E: Eczema / Atopic Dermatitis; NS: not specified

# Fig S2. Distribution of the studies per country and year of publication

Year-country.eps

The Y-axis represents the year of publication of the studies and the X-axis the country in which the study was conducted.

# Table S3. Methodology used in the included studies for each allergic disease

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Asthma | Rhinitis | Eczema | FA | Urticaria | Anaphylaxis |
|  | N=170 | N=70 | N=88 | N=42 | N=14 | N=7 |
| Questionnaire used,yes | 135(79.4) | 58(82.9) | 67(76.1) | 29(69.1) | 9(64.3) | 4(57.1) |
| Reference provided,yes | 57(42.2) | 26(44.8) | 26(38.8) | 6(20.7) | 1(11.1) | 0(0) |
| Quest administration: |  |  |  |  |  |  |
| Clinical examination alone (CE),yes | 6(4.4) | 3(5.2) | 6(9.0) | 1(3.5) | 1(11.1) | 1(25.0) |
| Personal interview alone (PI),yes | 25(18.5) | 7(12.1) | 8(11.9) | 3(10.3) | 1(11.1) | 2(50.0) |
| Self administered alone (SA),yes | 51(37.8) | 23(39.7) | 24(35.8) | 12(41.4) | 2(22.2) | 1(25.0) |
| Telephone alone (T),yes | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| CE;PI | 9(6,7) | 6(10.3) | 8(11.9) | 7(24.1) | 2(22.2) | 0(0) |
| CE;PI;SA | 3(2.2) | 1(1.7) | 2(3.0) | 0(0) | 0(0) | 0(0) |
| CE;PI;T | 2(1.5) | 1(1.7) | 1(1.5) | 0(0) | 0(0) | 0(0) |
| CE;PI;T;SA | 3(2.2) | 2(3.5) | 2(3.0) | 0(0) | 0(0) | 0(0) |
| CE;SA | 21(15.4) | 8(13.8) | 9(13.4) | 4(13.8) | 1(11.1) | 0(0) |
| CE;T | 1(0.7) | 1(1.7) | 1(1.5) | 0(0) | 0(0) | 0(0) |
| PI;SA | 12(8.9) | 4(6.9) | 3(4.5) | 0(0) | 0(0) | 0(0) |
| PI;T;SA | 1(0.7) | 1(1.7) | 1(1.5) | 1(3.5) | 1(11.1) | 0(0) |
| T;SA | 1(0.7) | 1(1.7) | 2(3.0) | 1(3.5) | 1(11.1) | 0(0) |
|  |  |  |  |  |  |  |
| *Atopy* |  |  |  |  |  |  |
| tIgE,yes | 78(45.9) | 31(44.3) | 45(51.1) | 24(57.1) | 8(57.1) | 4(57.1) |
| sIgE,yes | 51(30.0) | 32(45.7) | 41(46.6) | 28(66.7) | 10(71.4) | 7(100) |
| sIgE to food allergens,yes | 38(74.5) | 26(81.3) | 35(85.4) | 25(89.3) | 9(90.0) | 6(85.7) |
| Number of food allergens |  |  |  |  |  |  |
| 1 | 2(5.3) | 1(3.9) | 2(5.7) | 3(12.0) | 1(11.1) | 1(16.7) |
| 2 | 3(7.9) | 2(7.7) | 4(11.4) | 4(16.0) | 1(11.1) | 0(0) |
| 3 | 3(7.9) | 3(11.5) | 3(8.6) | 1(4.0) | 1(11.1) | 1(16.7) |
| 4 | 8(21.1) | 4(15.4) | 4(11.4) | 2(8.0) | 0(0) | 1(16.7) |
| 5 | 2(5.3) | 1(3.9) | 2(5.7) | 1(4.0) | 1(11.1) | 0(0) |
| 6 | 10(26.3) | 8(30.8) | 10(28.6) | 9(36.0) | 2(22.2) | 1(16.7) |
| 7 | 3(7.9) | 2(7.7) | 1(2.9) | 0(0) | 0(0) | 0(0) |
| 9 | 1(2.6) | 0(0) | 0(0) | 1(4.0) | 0(0) | 0(0) |
| 10 or more | 5(13.2) | 4(15.4) | 6(17.1) | 3(12.0) | 3(33.3) | 1(16.7) |
| Not reported | 1(2.7) | 1(3.9) | 3(8.6) | 1(4.0) | 0(0) | 1(16.7) |
|  |  |  |  |  |  |  |
| sIgE to aeroallergens,yes | 42(82.4) | 24(75.0) | 28(68.3) | 13(46.3) | 6(60.0) | 3(42.9) |
| Number ofaeroallergens |  |  |  |  |  |  |
| 1 | 1(2.4) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| 2 | 3(7.1) | 2(8.3) | 1(3.6) | 1(7.7) | 0(0) | 0(0) |
| 3 | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| 4 | 8(19.1) | 4(16.7) | 5(17.9) | 1(7.7) | 1(16.7) | 0(0) |
| 5 | 5(11.9) | 3(12.5) | 3(10.7) | 1(7.7) | 1(16.7) | 1(33.3) |
| 6 | 4(9.5) | 1(4.2) | 1(3.6) | 3(23.1) | 0(0) | 0(0) |
| 7 | 1(2.4) | 0(0) | 1(3.6) | 0(0) | 0(0) | 0(0) |
| 8 | 6(14.3) | 4(16.7) | 4(14.3) | 2(15.4) | 0(0) | 0(0) |
| 9 | 1(2.4) | 1(4.2) | 1(3.6) | 0(0) | 0(0) | 0(0) |
| 10 or more | 10(23.8) | 7(29.2) | 7(25.0) | 3(23.1) | 3(50.0) | 1(33.3) |
| Not reported | 4(9.5) | 2(8.3) | 5(17.9) | 2(15.4) | 1(16.7) | 1(33.3) |
|  |  |  |  |  |  |  |
| SPT,yes | 111(65.3) | 43(61.4) | 52(59.1) | 27(64.3) | 9(64.3) | 5(71.4) |
| SPT to food allergens,yes | 54(48.7) | 28(65.1) | 39(75.0) | 24(88.9) | 9(100) | 5(100) |
| Number of food allergens: |  |  |  |  |  |  |
| 1 | 4(7.4) | 1(3.6) | 1(2.6) | 2(8.3) | 0(0) | 1(20.0) |
| 2 | 11(20.4) | 4(14.3) | 6(15.4) | 1(4.2) | 0(0) | 0(0) |
| 3 | 7(13.0) | 6(21.4) | 6(15.4) | 5(20.8) | 2(22.2) | 1(20.0) |
| 4 | 7(13.0) | 5(17.9) | 5(12.8) | 1(4.2) | 0(0) | 1(20.0) |
| 5 | 7(13.0) | 4(14.3) | 4(10.3) | 3(12.5) | 2(22.2) | 0(0) |
| 6 | 5(9.3) | 2(7.1) | 2(5.1) | 1(4.2) | 0(0) | 0(0) |
| 7 | 5(9.3) | 3(10.7) | 5(12.8) | 4(16.7) | 3(33.3) | 1(20.0) |
| 8 | 1(1.9) | 0(0) | 1(2.6) | 0(0) | 0(0) | 0(0) |
| 9 | 2(3.7) | 1(3.6) | 1(2.6) | 2(8.3) | 0(0) | 0(0) |
| 10 or more | 3(5.6) | 2(7.1) | 6(15.4) | 4(16.7) | 2(22.2) | 1(20.0) |
| Not reported | 2(3.7) | 0(0) | 2(5.1) | 1(4.2) | 0(0) | 0(0) |
|  |  |  |  |  |  |  |
| SPT to aeroallergens,yes | 109(98.2) | 41(95.4) | 47(90.4) | 20(74.1) | 7(77.8) | 3(60.0) |
| Number of aeroallergens: |  |  |  |  |  |  |
| 2 | 3(2.8) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
| 3 | 8(7.3) | 3(7.3) | 2(4.3) | 0(0) | 0(0) | 0(0) |
| 4 | 7(6.4) | 3(7.3) | 4(8.5) | 3(15.0) | 1(14.3) | 0(0) |
| 5 | 9(8.3) | 2(4.9) | 3(6.4) | 2(10.0) | 0(0) | 0(0) |
| 6 | 10(9.2) | 2(4.9) | 3(6.4) | 0(0) | 0(0) | 0(0) |
| 7 | 17(15.6) | 5(12.2) | 7(14.9) | 4(20.0) | 2(28.6) | 0(0) |
| 8 | 8(7.3) | 3(7.3) | 2(4.3) | 0(0) | 0(0) | 0(0) |
| 9 | 7(6.4) | 5(12.2) | 5(10.6) | 4(20.0) | 1(14.3) | 0(0) |
| 10 or more | 34(31.2) | 16(39.0) | 18(38.3) | 6(30.0) | 3(42.9) | 3(100) |
| Not reported | 6(5.5) | 2(4.9) | 3(6.4) | 1(5.0) | 0(0) | 0(0) |
|  |  |  |  |  |  |  |
| Patch test,yes | 3(1.8) | 2(2.9) | 6(6.8) | 5(11.9) | not measured | not measured |
| Number of aeroallergens: |  |  |  |  |  |  |
| 2 | 0(0) | 0(0) | 1(16.7) | 0(0) | not measured | not measured |
| 3 | 0(0) | 0(0) | 1(16.7) | 1(20.0) | not measured | not measured |
| 4 | 1(33.3) | 1(50.0) | 0(0) | 1(20.0) | not measured | not measured |
| 7 | 0(0) | 0(0) | 1(16.7) | 1(20.0) | not measured | not measured |
| 8 | 1(33.3) | 1(50.0) | 1(16.7) | 1(20.0) | not measured | not measured |
| 25 | 0(0) | 0(0) | 1(16.7) | 1(20.0) | not measured | not measured |
| Not reported | 1(33.3) | 0(0) | 1(16.7) | 0(0) | not measured | not measured |
|  |  |  |  |  |  |  |
| FªHº of allergies |  |  |  |  |  |  |
| Mother,yes | 118(69.4) | 47(67.1) | 61(69.3) | 26(61.9) | 8(57.1) | 4(57.1) |
| Father,yes | 113(66.5) | 46(65.7) | 60(68.2) | 25(59.5) | 8(57.1) | 4(57.1) |
|  |  |  |  |  |  |  |
| *Lung function tests* |  |  |  |  |  |  |
| Spirometry,yes | 71(41.8) | 22(31.4) | 22(25.0) | 8(19.1) | 1(7.1) | 2(28.6) |
| Post bronchodilator test,yes | 13(18.3) | 4(18.2) | 2(9.1) | 1(12.5) | 0(0) | 1(50.0) |
| Peak flow,yes | 17(10.0) | 3(4.3) | 4(4.6) | 3(7.1) | 0(0) | 0(0) |
| BHR,yes | 59(34.7) | 19(27.1) | 19(21.6) | 6(14.3) | 1(7.1) | 1(14.3) |
| BHR method: |  |  |  |  |  |  |
| EVH(Eucapnic voluntary hyperpnoea) | 3(5.1) | 2(10.5) | 2(10.5) | 0(0) | 0(0) | 0(0) |
| Exercise | 6(10.2) | 3(15.8) | 3(15.8) | 3(50.0) | 0(0) | 0(0) |
| Histamine | 19(32.2) | 5(26.3) | 6(31.6) | 0(0) | 0(0) | 0(0) |
| Hypertonic Saline | 4(6.8) | 2(10.5) | 2(10.5) | 0(0) | 0(0) | 0(0) |
| Methacoline | 23(39.0) | 5(26.3) | 4(21.1) | 3(50.0) | 1(100) | 0(0) |
| Exercise;Histamine | 1(1.7) | 1(5.3) | 1(5.3) | 0(0) | 0(0) | 0(0) |
| Methacoline;Exercise | 2(3.4) | 1(5.3) | 1(5.3) | 0(0) | 0(0) | 1(100) |
| Methacoline;Hypertonic Saline | 1(1.7) | 0(0) | 0(0) | 0(0) | 0(0) | 0(0) |
|  |  |  |  |  |  |  |
| Biomarkers collected,yes | 41(24.1) | 14(20.0) | 16(18.2) | 10(23.8) | 3(21.4) | 2(28.6) |
| Disease severity measured,yes | 54(31.8) | 19(27.1) | 35(39.8) | 16(38.1) | 2(14.3) | 1(14.3) |
|  |  |  |  |  |  |  |
| *Health inequality* |  |  |  |  |  |  |
| Race,yes | 28(16.5) | 6(8.6) | 8(9.1) | 3(7.1) | Not measured | Not measured |
| Parental education,yes | 34(20.0) | 11(15.7) | 11(12.5) | 6(14.3) | 1 (7.1) | Not measured |
| SES,yes | 42(24.7) | 19(27.1) | 24(27.3) | 11(26.2) | 2(14.3) | Not measured |

Data are expressed as N(%); FA: food allergy; N refers to the number of studies assessing the specific allergic disease alone or in comorbidity

## 

## Table S4. Published classifications of asthma/wheeze in children

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Defining trait** | **Phenotype terms** | **Definitions** | **Characteristics** | **References** | **Comments** |
| **Symptoms with/without temporal pattern** | Transient early wheeze; Late-onset wheeze; Persistent wheeze | *Transient early wheeze*: (1) Children that had at least one lower respiratory tract illness with wheezing during the first three years of life but had no wheezing at six years of age; (2) Children that had no wheezing before the age of three years but had wheezing at the age of six years, (3) Children that had wheezing both before three years of age and at six years of age  *Late-onset wheeze*: (1) Children that had at least one lower respiratory tract illness with wheezing during the first three years of life but had no wheezing at six years of age; (2) Children that had no wheezing before the age of three years but had wheezing at the age of six years, (3) Children that had wheezing both before three years of age and at six years of age  *Persistent wheeze:* Children that had wheezing both before three years of age and at six years of age | *Transient early wheeze*: children that had diminished airway function (length-adjusted maximal expiratory flow at functional residual capacity [Vmax FRC]) both before the age of one year and at the age of six years, were more likely than the other children to have mothers who smoked but not mothers with asthma, and did not have elevated serum IgE levels or skin-test reactivity  *Late-onset wheeze*: did not have significantly elevated serum IgE levels as compared with those who had never wheezed and had lung function at the age of six whichwas within the normal range.  *Persistent wheeze*: were more likely than the children who never wheezed to have mothers with a history of asthma (P<0.001), to have elevated serum IgE levels (P<0.01) and normal lung function in the first year of life, and to have elevated serum IgE levels (P<0.001) and diminished values for Vmax FRC (P <0.01) at six years of age. | Leading reference: 177  Other: 3, 17, 22, 24, 36, 62, 75, 85, 98, 100, 104, 105, 118, 129, 131, 140, 150, 152, 157, 159, 161, 166, 168, 178, 180, 181, 186 | Some studies have used a similar approach but assessed them at different ages |
| Acute/Stable asthma | *Acute asthma (AA)*: had asthma diagnosed by a respiratory paediatrician based on clinical and lung function criteria and had an acute exacerbation of asthma, as described previously.  *Stable asthma (SA)*: had asthma diagnosed by a respiratory paediatrician based on clinical and lung function criteria and had no recent (past 4 weeks) respiratory infection, asthma exacerbation or medication change | In children AA the predominant phenotype was eosinophilic followed by mixed granulocytic.They had lower lymphocyte counts than SA, had greater lung function impairment than adult AA, and had significantly greater airflow obstruction, with lower FEV 1% predicted values than SA.  In children SA the predominant phenotype was the eosinophilic subtype, showed better lung function, with higher FEV1 % pred. values than adult SA. | 23; 194 |  |
| Chronic (persistent) asthma | *Chronic persistent asthma*: symptoms present more than twice a week for at least 3 consecutive months: a) Asthma symptoms limiting participation in daily activities (including sport and leisure); b) Nocturnal awakenings because of asthma symptoms | Chronic persistent asthma subgroup demonstrated significantly reduced lung function (PD20methacholine ≤0.14µmol), increased IgE, allergic poly-sensitization and impaired QoL, similar to that in patients pre-defined as Problematic severe asthma. | 97, 142 | Children with Chronic persistent asthma and those who are symptomatic predominantly during exacerbations may represent distinct phenotypes of childhood asthma with different clinical prognoses  Classification within the Chronic persistent asthma subgroup was found to be a significant explanatory factor for reduction in lung function, PAQLQ and increasing FENO, but not for BHR. |
| Intermittent asthma/wheeze | *Intermittent asthma*: Negative answers to the following questions: daytime symptoms > 1/week? Nighttime symptoms > 1/month? Treatment with inhaled steroid? | *Severe intermittent wheezing* as a distinct phenotype of wheezing during early childhood and is particularly characterized by more severe acute episodes requiring oral corticosteroids separated by asymptomatic periods.  *Mild intermittent asthma:* increased total IgE levels predict high eNO levels better than allergic sensitization in these children | 84, 170, 188 | These findings suggest that in preschool children with intermittent wheezing, episodes can be severe, with greater severity associated with previous episodes requiring oral corticosteroid use and with allergic sensitization.  Increasing total serum IgE but not SPT is associated with a highly significant increase in asthma severity score |
| **Factors/Trigger** | Multi-trigger wheeze; Episodic (viral) wheeze; Virus-associated/Viral wheeze | Episodic viral wheeze or Virus-associated wheeze: a) wheezing only during colds and not in the absence of colds  b) those children who wheezed only with discrete viral respiratory tract infections and were asymptomatic between episodes.  Multiple trigger wheeze:  a) wheeze in the absence of colds, irrespective of the presence or absence of wheeze with colds  b) those who wheezed with viral respiratory tract infections but were also symptomatic between episodes with other triggers, such as dust allergy, tobacco smoke, exercise, and cold air | *Virus-associated/Viral wheeze vs Multi-trigger wheeze*: more likely to be male, to be younger, and to have less frequent wheezy episodes. They were less likely to have night cough, shortness of breath or chest tightness, to have a personal or parental history of atopic disorders, to have a diagnosis of asthma, or to be receiving asthma treatment | 21, 36, 149, 169, 174 | Viruses were not reported. |
| Respiratory syncitial virus induced wheeze/bronchiolitis | RSV/(B or LRI): those with bronchiolitis characterized by widespread crepitations with or without wheeze; RSV/(W OR LRI): those with wheeze alone viral associated wheeze  \*rhinoviruses, other picornaviruses (coxsackie, echo, and enteroviruses), coronaviruses 229E and OC43, RSV, influenza A and B, parainfluenza viruses 1-3, adenoviruses, human metapneumovirus, Chlamydia pneumoniae, and Mycoplasma pneumoniae | *RSVW vs RSVB*: more likely to have evidence of allergic sensitization, more likely to have wheeze most days with colds, more likely to have ruttles and occasional ruttles most days with colds, 0.2,5.1). Cough was also more common both with colds, and have increased symptoms and increased use of inhaled steroids  . | 17, 173, 176 | Viruses were not reported (173). |
| Alternaria-positive asthma; Alternaria-negativeasthma | When compared with asthma among *Alternaria*-positive subjects,*Alternaria*-negative asthma is accompanied by lower levels of total IgE, independence from skin test reactivity to aeroallergens, greater prevalence of wheezing LRIs in the first year of life, earlier asthma diagnosis, and an increased asthma remittance rate by age 11 | *Alternaria-negative asthma vsAlternaria-positive asthma*: lower levels of total serum IgE, no relation to local aeroallergen skin tests, a younger age at diagnosis, greater remittance by age 11, and more frequent wheezing lower respiratory illnesses (LRIs) in the first year of life. | 182 | Viruses were not reported. |
| Solitary Exercise-induced bronchoconstriction | Exercise-induced asthma or exercise-induced bronchoconstriction (EIB) is typically characterized by a history of coughing or wheezing, or a history of shortness of breath with exercise | *Solitary EIB versus Chronic asthma with and without EIB*: There were no differences between groups in asthma severity, sex, present age, asthma onset age, EIB onset age, evolution time of asthma, eczema or food allergy. Atopic familiar disorders did not demonstrate differences except to familiar eczema group solitary EIB vschronic asthma without EIB. | 106 | Viruses were not reported. |
| **IgE sensitization** | Atopic and non-atopic asthma | *AA* children positive to SPT; *non-AA* children negative to SPT | *AA*: have more severe exacerbations of asthma in the previous year (ie, more emergency department visits and more oral corticosteroids courses) and have more frequent markers of atopy (nasal eosinophilia), allergic diseases (dermatitis) and steroids use.  *Non-AA*: have a significantly earlier onset of asthma, more past pneumonia episodes, and heavier tobacco consumption at home. | 16, 27, 30, 67, 113, 133, 137, 138, 151, 153, 165, 178, 185 |  |
| Monosensitised/polysensitised asthmatics | *Monosensitised/polysensitised asthmatics*: For each allergic children a score was done by adding the number of positive allergen at SPT. The score started from 1 (monosensitization) . | *Monosensitization*: predominant at age 3 and 7.  *Polisensitization*: predominant at age 11. The behavior of allergen sensitization seems to depend more on the age than on the period of symptom appearance | 54, 81 |  |
| **Inflammation** | Eosinophilic asthma/ Neutrophilic/ Mixed granulocytic/ Paucigranulocytic asthma | Eosinophilic asthma: subjects with >3% sputum eosinophils;  Non-eosinophilic asthma: patients without sputum eosinophilia  Neutrophilic asthma: those with >61% sputum neutrophils and <3%; Mixed granulocytic asthma: subjects with >61% sputum neutrophils and sputum >3% eosinophils; Paucigranulocytic asthma: those with <61% sputum neutrophils and <3% eosinophils | *Eosinophilic asthma vs Non-eosinophilic asthma*: more frequent moderate-to-severe asthma, higher blood eosinophil counts and serum eosinophil cationic protein, lower forced expiratory volume in 1 sec, the sputum eosinophil counts increased with increasing asthma severity. No significant differences were observed between the groups with regard to age, sex, family history of atopy, secondary smoking or asthma exacerbations.  In children acute asthma the predominant phenotype was eosinophilic followed by mixed granulocytic. In children stable asthma the predominant phenotype was the eosinophilic subtype. | 15, 23, 103 | These phenotypes served as the basis to distinguish acute and stable asthma in children (see *Symptoms with/without temporal pattern*) |
| **Severity** | Asthma/wheeze severity | *Mild asthma*: mild and infrequent asthma symptoms, symptom control with a β2-agonist p.r.n alone and need of a β2-agonist not exceeding 3 doses/week; *Mild wheeze*: without hospital admission or oral steroids and bronchodilator use on average less than three days per week in the absence of viral infections  *Moderate asthma*: had more frequent asthma symptoms and required more than 3 doses/week of a β2- agonist. These children were symptom-free when they received maintenance treatment with sodium cromoglycate or inhaled steroids at doses of 200-400 µg/day. With such maintenance treatment they had little need of extra β2- agonists (not exceeding 3 dose/week);  *Severe asthma*: had acute exacerbations in spite of treatment with low to moderate doses of inhaled steroids. They needed high doses of inhaled steroids or inhaled steroids in combination with a long-acting inhaled β2-agonist to be symptom-free (**112**); *Severe wheeze*: if a severe attack with a viral infection had occurred necessitating use of oral steroids or hospital admission, nights disturbed more than twice weekly, or exercise induced or nocturnal symptoms resulted in bronchodilator use more than an average of three days per week, in the absence of viral infections (**149**) | *Mild asthma:* usually began later in childhood, was episodic, and there was little or no evidence of airways obstruction between attacks. The attacks generally stopped before 10 years of age. IgE geometric mean values were lower compared to moderate and severe asthmatics.  *Moderate asthma*: had no evidence of endobronchial lesions or chronic aspiration.  *Severe asthma:* severe asthma exacerbation had significantly higher modified Pulmonary Index Score (MPISs) upon admission to the hospital and were significantly more likely to use ICS than children with acute asthma admitted to the ward, had significantly shorter durations of illness prior to being admitted to the hospital compared to those with a non-severe exacerbation. allergic or irritant triggers and a more rapid onset of illness were associated with more severe disease in this population.  Severe persistent asthma: onset usually in the first three years of life, a high frequency of attacks in the initial year, clinical and physiological evidence of persisting airways obstruction and pulmonary hyperinflation, chest deformity, and impairment of growth*.* | 2, 20, 49, 84, 112, 142, 149, 170, 175, 187, 188, 193, 194 | Severe asthma in children is associated with unique patterns of airway inflammation that persist despite corticosteroid treatment. However, no differences in sputum cellularity between the mild to moderate and severe asthma groups.  Neither the response to a direct nor an indirect challenge relates to the pattern or severity of symptoms in 5-6 year old children with active wheeze or a past history of wheeze. |
| **Treatment response** | Steroid-sensitive asthma; Steroid-insensitive asthma | SS asthmatic subjects were defined as those whose AM prebronchodilator FEV1 improved by greater than 15% after the GC burst; SI asthmatics: those failing to respond to the GC burst with a less than 15% improvement in their AM prebronchodilator FEV1 | *Steroid-sensitive asthma vs Steroid-insensitive asthma*:had a similar duration of asthma, they required oral GC therapy at a younger age, required a larger maintenance oral GC dose on admission, and were more likely to be African-American. Two distinct spirometry patterns were noted among the SI asthmatic subjects: “chaotic” and “non-chaotic.” Patients with the chaotic pattern were characterized by a significant degree of variability (greater than 30%) in daily pulmonary function, whereas those with nonchaotic, SI asthma were characterized by less than 15% variability in daily lung function, and treated with oral GCs at a later age. | 179 |  |
| Difficult-to-treat asthma | The physician considered their asthma difficult to treat assessed on specified parameters (i.e., complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations, and/or unresponsive to therapy) | Mostly male in the pediatric and adolescent patients (in adults female were predominant), younger patients have higher IgE levels. In children, IgE levels increase with increasing asthma severity. Pediatric patients with severe disease have higher mean IgE levels (280.2 IU/mL) than those with moderate disease (145.8 IU/mL) or mild disease (137.8 IU/mL). A similar trend is seen in adolescent patientsbut did not reach statistical significance. | 187 |  |
| Well-controlled asthma | Those asthmatics who were not included in the Exacerbations or Chronic persistent asthma | Used as a control group (see Chronic persistent asthma and problematic severe asthma) | 97 |  |
| **Comorbidity** | Wheezing with rhinoconjunctivitis (RCW);Wheezing with rhinitis (RW) | RW and RCW were defined as having rhinitis and rhinoconjunctivitis in the past year, respectively, in addition to current wheezing symptoms | *Associations with RW*: Male gender, history parental asthma and/or rhinitis, presence of dampness and mold in the house lived in during the first year of life and over the past year, living in a one-room house, monthly family income of <350 US$, history of maternal smoking during pregnancy, exposure to smoke in the house over the past year, and presence of atopic dermatitis.  *Associations with RCW*: history of parental asthma and/or rhinitis, presence of dampness and mold in the house lived in during the first year of life and over the past year, living in a one room house, monthly family income of <350 US$ history of maternal smoking during pregnancy, exposure to smoke in the house over the past year, and presence of atopic dermatitis. Additionally, duration of breastfeeding per additional month was found to be independent risk factors for RCW. | 138 |  |
|  | Asthma without allergy; Asthma with allergy (hay fever, rhinitis, dermatitis, neurodermatitis) | Children were classified as having asthmatic disease, when a positive response was obtained to individually delineated questions with regard to the specific diagnoses, summarized here as “Has a physician ever diagnosed asthma, asthma bronchiale, asthmatic or spastic bronchitis in your child?”. Allergic disorders were defined as a positive answer to “Has a physician ever diagnosed allergies, hay fever, allergic rhinitis, atopic dermatitis, neurodermitis, etc. in your child?”. As it was known that a formal diagnosis of “allergies” was not readily made by local physicians, additional questions were concerned with a child's symptomatology and the parents' assessment of their child's allergy status. | Asthma without a reported diagnosis of allergies or symptoms was much more prevalent than expected and was reported more frequently in areas with coal-heating; Asthma with allergies was less prevalent occurred more often in areas with heavy traffic and district heating. | 63 | This suggests that environmental exposures (i.e., complex pollution mixtures associated with residential coal-heating and/or traffic) may have differentially influenced the phenotypic expression of asthma. |
| AE + EIA; AD and current asthma; AD and wheeze; Eczema-asthma syndrome |  |  | 65, 141, 143, 148 | See table 3 |

## Table S5. Published classifications of eczema/atopic dermatitis in children

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Defining trait** | **Phenotype terms** | **Definitions** | **Characteristics** | **References** | **Comments** |
| **Symptoms with/without temporal pattern** | Early-onset intermittent AD; Late-onset intermittent;Intermittent eczema | *Early-onset intermittent AD*: before 18 months of age  *Late-onset intermittent AD*: 18–42 months of age  *Intermittent eczema*: those who have a diagnosis of eczema after the age of 36 months but not every year | *Early-onset intermittent AD*: Levels of total IgE at 8, 12 and 18 months of age were associated with early onset of *AD.* | 124; 164 | Early measurement of total immunoglobulin E is of little clinical use in predicting subsequent risk of visible eczema |
| Early AD; Transient eczema; Persistent AD/eczema; Late-onset eczema | *Early AD*: onset of disease in the first 2 years of life  *Transient eczema*: those with a diagnosis of eczema before 36 months of age  *Persistent eczema*: those with a diagnosis of eczema throughout the study from baseline until follow-up  *Late-onset eczema*: those with a diagnosis of eczema after 36 months of age | *Early AD:* is associated with asthma at school age, but in many of these asthmatic children, wheezing manifests before or with the onset of AD.  *Transient eczema*: are less associated with asthma and AR at age 7  *Persistent eczema*: highly associated with asthma and AR at age 7 years but to a lesser extent than those with late-onset eczema.  *Late-onset eczema*: is particularly highly associated with asthma and AR at age 7 years. | 65, 70, 79, 124, 164 | Major determinants of the prognosis of early AD were severity of disease and early atopic sensitization |
| **Factors/Trigger** | - | | | | |
| **IgE sensitization** | Allergic contact dermatitis | Contact allergy confirmed by a clinically relevant positive patch test result in combination with exposure history, dermatitis history and dermatitis pattern (if present at the time point of the examination) | *ACD*: often coexist with atopic eczema and half of ACD children have flexural eczema, while lacking features sufficient for the diagnosis of AE according to Hanifin and Rajka | 99 | It is an actual problem to differentiate between ACD and atopic eczema on morphological grounds. Morphological features and localization of eczema must always be carefully considered in the broad context of the patient’s history and present status (stigmata of atopy, features of contact sensitization or irritation, comorbidities, functional status of the skin, etc.) |
| Extrinsic AE; Intrinsic AE | Children with and without a reported physician’s diagnosis of asthma or wheezing ever; with (EAE) or without (IAE) atopic sensitization [IgE antibodies to common food (fx5) and/or common inhalant (Phadiatop) allergens’; with or without atopic sensitization to either common food or inhalant allergens; or with and without symptoms or a reported physician’s diagnosis of rhinoconjunctivitis. | The determinants of EAE and IAE did not differ. However, evere LRTI in the first 2 years of life and usage of antibiotics ever were found to be positively related only to AE with asthma, whereas the effect of LRTI on AE without asthma had an opposite effect. | 196 | They identified two phenotypes of AE according to the presence and absence of a diagnosis of asthma and wheeze ever with different risk factors. This differentiation may be more relevant than EAE and IAE to determine the heterogeneity of AE. |
| **Inflammation** | - | | | | |
| **Severity** | Mild AD; Moderate AD; Severe AD | *AD severity*: using objective SCORAD which includes the assessment of two items in a standardized manner: (a) extent (applying the rule of nine) and (b) intensity (erythema, edema/papulation, oozing/crust, excoriation, lichenification and dryness on a scale from 0 to 3). The severity of AD was subsequently categorized into mild (<15 SCORAD points), moderate (15-40 SCORAD points), and severe (>40 SCORAD points) according to the objective components of the index (clinical signs and disease extent), ranging from 0 to 83 points16 (i.e., excluding subjective components pruritus and sleeplessness from the SCORAD index) | Children with severe atopic dermatitis and high IgE levels are at risk for sensitization to food allergens and aeroallergens. There is a correlation between SCORAD index and total serum IgE.  Children with AD whose eczema started during the first year of life were more likely to have severe disease than were those whose eczema started later; a history of atopy (asthma, hay fever, or both) was associated with severe AD; and children with AD who lived in an urban area were at increased risk of severe disease compared with their counterparts who lived in a rural environment.  AD severity worsens when there is an early sensitization to cow's milk or to egg. | 37,64,163,195 | Severity of AD declined with age, with an increased fraction of mild cases and a reduced fraction of moderate severity and no obvious sex difference (37). However, in other studies severity of AD increased with age (64). Those with eczema that commenced during the first year of life, which was accompanied by asthma, hay fever, or both, and associated with living in an urban area, had more severe disease independent of other potential risk factors |
| **Treatment response** | - | | | | |
| **Comorbidity** | AE + EIA; AD and current asthma; AD and wheeze; Eczema-asthma syndrome  Food allergy and atopic eczema; AD with food hypersensitivity; Transient food allergy + AD; Persistent FA + AD  AD + comorbidities (asthma, allergic rhinoconjunctivitis, urticarial) | *AE + EIA*: atopic eczema was made on clinical grounds; a personal or family history of atopy, flexural distribution, and severe pruritus with lichenification and EIA defined according to the percentage fall in peak expiratory flow-rate (PEFR) after exercise;  *AD and current asthma*: AD defined according to Hanifin and Radja criteria and with a diagnosis of asthma by a doctor and symptomatic during the past year that had improved with asthma medication; *AD and wheeze*: AD present if at least one of the following applied: (1) reported diagnosis by the family physician, (2) parental reporting of symptoms of AD, and (3) visible AD at the time of follow-up and any wheezing in the past 12 months;  *Eczema-asthma syndrome*: infants have a familial tendency to respond immunologically to specific antigens in such a way as to become abnormally sensitive to that antigen (and perhaps others) | *AD and wheeze:* Children have a marked loss in lung function.  *AE + EIA*: eczematous children with a history of wheezing have exercise-induced asthma which distinguishes them from AE only. Patients with eczema and no evidence of EIA, normal levels of IgE, and lack of skin sensitivity may well constitute a separate group with a different pathophysiological mechanism for their eczema. | 39, 45, 65, 66, 114, 141, 143, 148, 196 | Early comanifestation of these atopic phenotypes rather than a progressive atopic march.  See table of FA for Food allergy and atopic eczema; AD with food hypersensitivity; Transient food allergy + AD; Persistent FA + AD |

## Table S6. Published classifications of rhinitis/allergic rhinitis in children

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Defining trait** | **Phenotype terms** | **Definitions** | **Characteristics** | **References** | **Comments** |
| **Symptoms with/without temporal pattern** | Seasonal rhinoconjunctivitis and Perennial rhinoconjunctivitis (*Upper-airway allergy)* | *Upper-airway allergy*: seasonal or perennial rhinoconjunctivitis, symptoms of sneezing, redness, itching and tearing of the nose or eyes and/or respiratory complaints. Diagnosis was confirmed by the presence of specific IgE in the plasma (**128**)  *Seasonal allergic rhinitis (SAR)*: he reported seasonal symptoms had to be associated with the respective seasonal sensitization to birch or grass pollen. This specific sensitization had to be detectable notlater than 1 year after the occurrence of symptoms. | Children in which SAR had already developed in the second year all were born in spring or early summer, resulting in at least two seasons of pollen exposure before manifestation of SAR. Risk factors were male sex, atopic mothers and fathers having allergic rhinitis themselves, first-born child, early sensitization to food, and atopic dermatitis. Early wheezing was not associated with SAR. | 59, 128 | The prevalence of upper-airway allergy in the children started to develop after 12 months of life Food-specific antibodies were associated with upper-airway allergy. |
| **Factors/Trigger** | Related to IgE sensitization to food and/or inhalant allergens | | | | |
| **IgE sensitization** | Allergic rhinitis; Non-allergic rhinitis; | *Allergic rhinitis*: defined as a significant problem with sneezing, blocked or runny nose in the past 12 months in periods without accompanying cold or flu with relevant allergic sensitization against ≥1 inhaled allergens (i.e. symptoms during exposure;  *Non-allergic rhinitis*: rhinitis with irrelevant sensitization (i.e. no symptoms during exposure) or no sensitization; | *Allergic rhinitis vs Non-allergic rhinitis*:Sensitization to inhaled allergens at an early age (4 years) precedes the development of allergic rhinitis, whereas symptoms of rhinitis do not. Among 4- and 8-year-olds, allergic rhinitis and nonallergic rhinitis were associated with asthma, eczema, and food hypersensitivity. Twenty-five percent of 8-year-olds with allergic rhinitis also had oral allergy syndrome. | 32, 40, 42, 44, 56, 68, 71, 84, 87, 95, 96, 100, 102, 114, 115, 122 |  |
| **Inflammation** | - | | | | |
| **Severity** | Chronic rhinitis (plus allergic rhinitis) | *Chronic rhinitis*: defined by the presence of episodes of rhinorrhea, post-nasal drip, throat irritation and nasal congestion/blockage and/or attacks of sneezing (apart from periods with colds) that are present on most days for >4 weeks in the past year.  *Allergic rhinitis (AR)*: was defined as a history of any of these symptoms concomitant with a positive SPT. concomitant with a positive SPT; *Non-allergic rhinitis (NAR)*: same as above but with negative SPT | AR is more common in male children, is relatively rare below the age of 2 years, and accounts for two-thirds of all childhood chronic rhinitis and 73.3% of all chronic rhinitis in school-aged children (≥ 6 years old). Children with AR have greater drug hypersensitivity to antipyretic medications; were more likely to have more severe atopic, eye and nasal symptoms, and to require adjunct therapy with inhaled corticosteroids; and were at a greater risk of asthma-related events and hospitalization.  Children with NAR were more likely to be treated with a leukotriene antagonist and had more sleep awakening.  Children with AR experienced more moderate to severe symptoms (nasal itch, sneezing, nasal congestion, and discharge) compared to pre-schoolers with NAR. Sleep awakening predominated in the NAR group at all ages, with symptoms worsening in the older age group. | 101 |  |
| **Treatment response** | - | | | | |
| **Comorbidity** | Wheezing with rhinoconjunctivitis (RCW);Wheezing with rhinitis (RW) | *Wheezing with rhinoconjunctivitis (RCW)*: having rhinoconjunctivitis in the past year, respectively, in addition to current wheezing symptoms  *Wheezing with rhinitis (RW)*: having rhinitis in the past year, respectively, in addition to current wheezing symptoms |  | 138 | See comorbidities in Asthma |

## Table S7. Published classifications of food allergy in children

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Defining trait** | **Phenotype terms** | **Definitions** | **Characteristics** | **References** | **Comments** |
| **Symptoms with/without temporal pattern** | FHS; Transient FHS; Intermittent FHS; Late onset FHS; Persistent FHS | *Food hypersensitivity (FHS)*: symptoms related to ingestion of a certain food such as wheeze, itchy eyes and/or runny nose, facial edema, urticaria, eczema or vomiting/diarrhea  *Transient FHS*: symptoms\* between 1 and 4 years of age but not thereafter;  *Intermittent FHS*: symptoms\* at 1 and/or 2 years, not at 4 years, but again at 8 years;  *Late-onset FHS*: symptoms\* at 4 and 8 years or at 8 yearsonly;  *Persistent FHS*: symptoms\* at 1 and/or 2 years, and 4 and 8 years of age. \*parentally reported symptoms related to ingestion of a certain food were defined as FHS: wheeze, itchy eyes and/or runny nose, facial edema, urticaria, eczema or vomiting/diarrhea | Children with persistent FHS significantly more often reported occurrence of wheeze, itchy eyes/runny nose, urticaria and eczema as symptoms caused by foods as compared with children with transient FHS. Children with persistent FHS exhibited significantly higher IgE-ab levels to food at both 4 and 8 years of age  as compared with the other phenotypes combined. The pattern of sensitization was very similar in children who never had FHS and children with transient FHS. One-third of the children with persistent FHS children reported to have symptoms related to egg, whereas only 4% of children with late-onset FHS reported egg-related symptoms, and the corresponding figure for intermittent FHS was 10%. Transient, intermittent and persistent FHS, all with an onset before 4 years of age, significantly increased the OR for asthma, AR and eczema at 8 years of age (with the exception of intermittent FHS and eczema). | 39, 120 |  |
| **Factors/Trigger** | Cow’s milk allergy; Peanut allergy; Wheat allergy | *Cow’s milk allergy*: Children with clinical symptoms (urticaria, atopic dermatitis, repeated wheezing episodes, failure to thrive, vomiting, diarrhea, and bloody stools) which ceased upon dietary elimination of cow’s milk proteins and re-appeared on open challenge.  *Peanut allergy*: positive answer to the following question in the 8-year-questionnaire regarding the latest 12-month period: ‘Is your child allergic to any food item?’. Symptom options were ‘nose/eyes symptoms’, ‘mouth-itching’, ‘breathing problems’, ‘vomiting/diarrhea’, ‘eczema’, ‘urticaria’. Reactions to peanut had to be indicated on at least one of these symptoms or reported as ‘excluded from the diet during the last 12 months because of previous symptoms’.  *Wheat allergy*: clinical history consistent with an IgE-mediated allergic reaction on wheat ingestion and a positive wheat IgE test result. | *Cow’s milk allergy*: Gastrointestinal complaints in children with CMA in infancy continue to be common at 10y of age. Although the immediate CMA of infancy had remitted in most of the children by the age of 10y, the subjects suffered from a wide variety of atopic manifestations or consequences, including a high frequency of respiratory allergy, positive skin prick tests and recurrent otitis. Moreover, dose-dependent gastrointestinal milk intolerance seems to persist in a certain proportion of these children. children with CMA achieved tolerance at an age significantly higher than the children with egg or wheat allergy.  *Peanut allergy*: Peanut symptoms were more severe in children with Ara h 1, 2 or 3 reactivity. Children with IgE reactivity both to Ara h 2 and to Ara h 1 or 3 more often reported peanut symptoms than children with IgE only to Ara h 2, particularly respiratory symptoms.  *Wheat allergy*: wheat IgE level was an important prognostic factor predicting resolution of wheat allergy. Wheat IgE levels differed overall in the groups that outgrew wheat allergy compared with those individuals who remained allergic by the end of follow-up, and wheat IgE levels predicted the rate of resolution of allergy. | 46, 73, 83, 121, 191, |  |
| Clinically reactive to all forms of milk; Tolerant to heated milk (HM) products; Outgrown milk allergy | *Clinically reactive to all forms of milk*: patients with milk allergy reactive to all forms of milk products  *Tolerant to heated milk (HM) products*: intermediate group of patients with milk allergy who tolerated heated milk (HM) in the form of muffins, waffles, and pizza but reacted to regular cow’s milk ;  *Outgrown milk allergy*: patients with milk allergy who have outgrown their milk allergy | IgE from patients who have outgrown their milk allergy tended to bind fewer milk peptides compared with IgE from those with persistent milk allergy.  IgE from HM-tolerant subjects bound significantly fewer IgE peptides than that from the allergic group and bound fewer peptides with IgG4 than either those who had outgrown their milk allergy. | 192 |  |
| Cow milk allergy immediate reactors (to cow milk challenge) ; Cow milk allergy delayed reactors | Cow milk allergy immediate reactors (to cow milk challenge): onset of symptoms within 2 minutes up to 2 hours; Cow milk allergy delayed reactors: presenting a history of symptoms after a delay of more than 2 hours | *Delayed vs immediate reactors*: They were younger, the interval between last reaction and study entry was shorter, they manifested their first symptom very early in infancy, within the first month of life and were given cow milk protein containing formulas in the first 2 months of life. | 28 |  |
| **IgE sensitization** | IgE-mediated CMA; non-IgE-mediated CMA; | CMA confirmed by using an elimination challenge test and IgE positivity or negativity to CM (determined to be positive by means of SPT, CAP, or both) | *IgE-mediated CMA vs non-IgE-mediated CMA*: had more frequent asthma, rhinoconjunctivitis, atopic eczema, and sensitization to any allergen, less tolerant to CM at all time points. Urticaria, exanthema, or both were more common, whereas for non-IgE mediated CMA AE and diarrhea were more common. | 50 |  |
| IgE-mediated FA | Children were diagnosed as having IgE-mediated food allergy when they fulfilled both of the following criteria:  1. Presence of specific IgE to at least one type of food as shown by elevated titers of specific IgE (>0.35kU/L) or positive skin-prick test.  2. A consistent and clear-cut history of food-related symptoms that developed in early phase after the ingestion of a certain food or positive open food challenge. | In 189 children (60%)  there was a consistent and clear-cut history relating a specific food type with symptoms and, moreover, 82 (26%) children had a history of anaphylaxis after the incriminating food exposure whereas in the remaining 126 (40%) children, an open challenge test was necessary to confirm the diagnosis of IgE-mediated food allergy. The majority of the children presented with cutaneous symptoms (94%; eczema, urticaria, and angioedema) followed by respiratory symptoms (30.2%; wheezing, dyspnea, rhinitis, cyanosis, and hoarseness), gastrointestinal symptoms (19.4%; oral pruritus, nausea, vomiting, abdominal cramping, and diarrhea), neurological symptoms (2.9%; dizziness, headache, and confusion), and cardiovascular symptoms (1.3%; hypotension, tachycardia, and bradycardia). | 139 | Children with isolated egg allergy have a lower rate of respiratory allergies, whereas children with tree nuts–peanut allergy have a higher rate of pollen but not dust-mite sensitization and a higher rate of asthma. The data also suggest that multisensitized children have a more severe clinical presentation including higher risk of anaphylaxis. |
| **Inflammation** | - | | | | |
| **Severity** | - | | | | |
| **Treatment response** | - | | | | |
| **Comorbidity** | Food allergy and atopic eczema; AD with food hypersensitivity; Transient food allergy + AD; Persistent FA + AD  Oral allergy syndrome | *AD with FHS*: AD diagnosed according to Hanifin-Rajka criteria and FHS when parents reported any adverse reactions to foods in the interview or when a child had a positive outcome in at least one of the follow-up test procedures; food-specific SPT ≥ 3 mm or food-sIgE ≥ class 1; all without a clear-cut negative case history, i.e., the child regularly consumed the culprit food without any symptoms  *Transient FA + AD*: positive first challenge and negative second challenge in AD patients defined by the criteria of Sampson and Seymour modified from Hanifin and Rajka  *Persistent FA + AD*: positive first and positive second challenge in AD patients defined by the criteria of Sampson and Seymour modified from Hanifin and Rajka  *Oral allergy syndrome (OAS)*: itchy mouth from eating apple, peach, kiwi, banana, or raw carrot. | *AD with FHS*: Immediate-type reaction to cow’s milk challenge was associated with SPT positivity, while delayed reactions were related to patch positivity. In infants with positive SPT for cow’s milk, this reaction also tended to occur concomitantly with positive SPT for egg and wheat.  *Transient vsPersisitent FA + AD*: specific IgE as well as total IgE in serum was significantly higher in the persistent FA + AD children, although there was an inconsistent pattern looking at single allergens and there were no significant longitudinal changes between the groups.  *Oral allergy syndrome*: common among school-aged children with allergic rhinitis who are sensitized to birch. | 39, 45, 66, 122 | Food allergy and atopic eczema: not defined |

## Table S8. Published classifications of urticaria in children

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Defining trait** | **Phenotype terms** | **Definitions** | **Characteristics** | **References** | **Comments** |
| **Symptoms with/without temporal pattern** | Single-episode acute urticaria; Recurrent acute urticaria | If the duration of symptom-free periods between urticaria episodes is longer than 6 weeks and if the episodes last less than 6 weeks, urticaria is considered to be “recurrent acute | Angioedema was present in 37.5% of those with the acute single-episode type, in 54% of those with recurrent urticaria. An infectious agent was discovered in 58% of patients in the acute single-episode group, in 31% of patients in the acute recurrent group. | 135 |  |
| **Factors/Trigger** | - | | | | |
| **IgE sensitization** | - | | | | |
| **Inflammation** | - | | | | |
| **Severity** | Acute urticaria; Chronic urticaria | Acute urticaria defined by the recurrence of the lesions over a time period of less than 6 weeks, while chronic urticaria is defined as wheals continuously or intermittently occurring for at least 6 weeks | *Chronic vs acute urticaria*: included older children and more boys, physical factors were the leading cause whereas in acute urticaria infection was the most frequently documented cause, followed by drugs, and food allergies. The frequency of the patients with a personal history of other allergic diseases (allergic rhinitis, asthma, and atopic dermatitis) was similar between the acute and chronic groups, and the most common disease was allergic rhinitis in both groups. There were no statistical differences in total IgE production, positive sensitization to specific allergens and eosinophil percentages between the patients with acute and chronic urticaria. Angioedema was more generalizedin chronic urticaria. | 53, 123, 135 |  |
| **Treatment response** | - | | | | |
| **Comorbidity** | Urticaria with atopic dermatitis; Urticaria without AD/eczema | *Urticaria with atopic dermatitis*: Elevated, itchy hives resembling mosquito bites or blisters “blisters”, coming and going, usually disappearing in 1 or 2 days and Dry skin and itchy rash with typical distribution (face/outer limbs/folds of elbows or behind knees/wrists or fronts of ankles) for ≥ 2 weeks; or doctor’s diagnosis of eczema | Both history and diagnosis of urticaria was significantly associated in AD children compared to non AD children, and the frequency of urticaria was particularly higher when the AD started during the first year of life. Not all the cases of urticaria in AD children were related to food allergy. The increased frequency of urticaria was observed among children with food reactions but also among children with increased rate of infections, indicating that urticaria may be caused by both allergic and nonallergic mechanisms | 31, 115 |  |

# Table S9. Terms used to examine phenotypes in studies assessing single allergic diseases

|  |  |  |  |
| --- | --- | --- | --- |
| **Allergic disease** | **Classification** | **Terms/Phenotypes** | **References** |
| Anaphylaxis | Factors/Trigger | Food-dependent IgE-mediated anaphylaxis; Drug-dependent anaphylaxis; Hymenoptera venom-dependent anaphylaxis; Exercise-induced food-dependent anaphylaxis, Vaccine-dependent anaphylaxis; Latex anaphylaxis; Additive anaphylaxis;Immunotherapyanaphylaxis;Idiopathic anaphylaxis | [77] |
| Eczema / Atopic Dermatitis | Related term | Atopic Eczema | [35,58,99] |
| Eczema / Atopic Dermatitis | Related term | Atopic Dermatitis | [34,38,79] |
| Eczema / Atopic Dermatitis | IgE sensitization | Allergic contact dermatitis | [99] |
| Eczema / Atopic Dermatitis | IgE sensitization | Intrinsic AD | [117] |
| Eczema / Atopic Dermatitis | IgE sensitization | Extrinsic AD | [117] |
| Eczema / Atopic Dermatitis | Severity | Mild AD | [37] |
| Eczema / Atopic Dermatitis | Severity | Moderate AD | [37] |
| Eczema / Atopic Dermatitis | Severity | Severe AD | [37,64,163] |
| Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Incident AD | [70] |
| Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Remittent AD | [70] |
| Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Recurrent AD | [70] |
| Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Early-onset intermittent AD | [164] |
| Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Late-onset intermittent AD | [164] |
| Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Persistent AD | [70,79,164] |
| Food Allergy | Symptoms with or without temporal pattern | Doctor-diagnosed Food allergy | [69] |
| Food Allergy | Factors/Trigger | Cow's milk allergy | [73] |
| Food Allergy | Factors/Trigger | Peanut allergy | [121] |
| Food Allergy | Factors/Trigger | Clinically reactive to all forms of milk;Tolerant to heated milk (HM) products;Outgrown milk allergy | [192] |
| Rhinitis | IgE sensitization | Allergic rhinitis | [40] |
| Rhinitis | IgE sensitization | Non-allergic rhinitis | [40] |
| Urticaria | Severity | Acute Urticaria | [53,135] |
| Urticaria | Severity | Chronic urticaria | [135] |
| Urticaria | Symptoms with or without temporal pattern | Recurrent acute urticaria | [135] |
| Asthma and/or wheeze | Inflammation | Eosinophilic bronchitis | [15] |
| Asthma and/or wheeze | Inflammation | Eosinophilic asthma | [103] |
| Asthma and/or wheeze | Inflammation | Non-eosinophilic asthma | [103] |
| Asthma and/or wheeze | IgE sensitization | Wheezy bronchitis | [108,112,145,151] |
| Asthma and/or wheeze | IgE sensitization | Atopic asthma | [16,30,113,133,151,153] |
| Asthma and/or wheeze | IgE sensitization | Non-atopic asthma | [16,27,30,113,133] |
| Asthma and/or wheeze | IgE sensitization | Atopic wheeze | [67,165] |
| Asthma and/or wheeze | IgE sensitization | Non-atopic (never) wheeze | [67,165,178] |
| Asthma and/or wheeze | IgE sensitization | Atopic wheezy bronchitic | [153] |
| Asthma and/or wheeze | IgE sensitization | Non-atopic wheezy bronchitic | [153] |
| Asthma and/or wheeze | IgE sensitization | Early-onset non-atopic asthma | [137] |
| Asthma and/or wheeze | IgE sensitization | Monosensitised asthmatics | [54,81] |
| Asthma and/or wheeze | IgE sensitization | Polysensitised asthmatics | [54,81] |
| Asthma and/or wheeze | Related term | Current asthma | [9,12,17,60,190] |
| Asthma and/or wheeze | Related term | Current asthma with positive BHR | [10] |
| Asthma and/or wheeze | Related term | Current physician-diagnosed atopic asthma | [185] |
| Asthma and/or wheeze | Related term | Current physician-diagnosed non-atopic asthma | [185] |
| Asthma and/or wheeze | Related term | Current wheeze | [4,16,22,60,152,168] |
| Asthma and/or wheeze | Related term | Current BHR | [60] |
| Asthma and/or wheeze | Related term | current cough | [152] |
| Asthma and/or wheeze | Related term | Recent wheeze | [4,12,150] |
| Asthma and/or wheeze | Related term | Occasional wheeze | [76,109] |
| Asthma and/or wheeze | Related term | Recurrent wheeze | [25,94,109] |
| Asthma and/or wheeze | Related term | Resolved physician-diagnosed asthma | [185] |
| Asthma and/or wheeze | Related term | Late-onset cough | [152] |
| Asthma and/or wheeze | Related term | Persistent cough | [152] |
| Asthma and/or wheeze | Related term | New-onset wheeze | [29] |
| Asthma and/or wheeze | Related term | Early life wheezing | [190] |
| Asthma and/or wheeze | Related term | Late life wheezing; | [190] |
| Asthma and/or wheeze | Related term | Wheeze with atopy and BHR | [146] |
| Asthma and/or wheeze | Related term | Past wheeze | [149] |
| Asthma and/or wheeze | Related term | Ex-wheeze | [150] |
| Asthma and/or wheeze | Related term | Early childhood atopics | [171] |
| Asthma and/or wheeze | Related term | Chronic childhood atopics | [171] |
| Asthma and/or wheeze | Related term | Persistent asymptomatics | [150] |
| Asthma and/or wheeze | Related term | Wheezing ex-coughers | [150] |
| Asthma and/or wheeze | Related term | Wheeze | [13,15,27,47,90,93,144,154,155,178] |
| Asthma and/or wheeze | Related term | Asthma | [14,43,47,72,75,90,93,108,127,134,144,145,178,183] |
| Ever asthma | [113] |
| Diagnosis of asthma ever | [60] |
| Active asthma | [27] |
| Asthma and/or wheeze | Related term | Diagnosed asthma | [4,12,130,152] |
| Asthma and/or wheeze | Related term | Obstructive airways disease (OAD) | [94] |
| Asthma and/or wheeze | Related term | BHR | [72,92] |
| Asthma and/or wheeze | Related term | Cough | [15,155] |
| Asthma and/or wheeze | Related term | Respiratory symptoms | [4] |
| Asthma and/or wheeze | Related term | Frequent respiratory symptoms with no asthma diagnosis | [185] |
| Asthma and/or wheeze | Related term | Chest cold | [15] |
| Asthma and/or wheeze | Related term | Childhood asthma | [60,184] |
| Asthma and/or wheeze | Related term | Childhood wheeze | [171] |
| Asthma and/or wheeze | Related term | Infantile asthma | [52] |
| Asthma and/or wheeze | Related term | Infantile bronchiolitis | [127] |
| Asthma and/or wheeze | Related term | Infancy wheeze | [11] |
| Asthma and/or wheeze | Related term | Post infancy wheeze | [11] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Intermittent asthma | [170] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Early (transient) wheeze | [17,62,85,98,104,118,129,131,140,157,161,166,168,177,178,180,181,186] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Late-onset wheeze | [17,62,85,98,104,129,131,152,157,161,166,177,181,186] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Persistent wheeze | [17,22,36,62,75,85,98,104,129,131,140,150,152,157,161,166,177,180,181,186] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Early-onset persistent wheeze | [118,162,168] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Late-onset persistent wheeze | [118,162,168] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Acute asthma | [23,194] |
| Asthma and/or wheeze | Symptoms with or without temporal pattern | Stable asthma | [23] |
| Asthma and/or wheeze | Severity | Mild asthma | [2,112] |
| Asthma and/or wheeze | Severity | Mild-moderate asthma | [175] |
| Asthma and/or wheeze | Severity | Moderate asthma | [112,193] |
| Asthma and/or wheeze | Severity | Severe asthma | [112,175,193] |
| Asthma and/or wheeze | Severity | Asthma with severe exacerbations | [194] |
| Asthma and/or wheeze | Severity | Mild wheeze | [149] |
| Asthma and/or wheeze | Severity | Moderate wheeze | [149] |
| Asthma and/or wheeze | Severity | Mild-persistent asthma | [170] |
| Asthma and/or wheeze | Severity | Moderate-persistent asthma | [170] |
| Asthma and/or wheeze | Severity | Severe-persistent asthma | [2,170] |
| Asthma and/or wheeze | Severity | Severe early childhood wheeze | [49] |
| Asthma and/or wheeze | Severity | Severe intermittent wheezing | [188] |
| Asthma and/or wheeze | Factor/Trigger | Episodic (viral) wheeze | [21,36,174] |
| Asthma and/or wheeze | Factor/Trigger | Multi-trigger wheeze | [21,169,174] |
| Asthma and/or wheeze | Factor/Trigger | Virus-associated wheeze | [169] |
| Asthma and/or wheeze | Factor/Trigger | Respiratory syncitial virus induced bronchiolitis (RSVB) | [173] |
| Asthma and/or wheeze | Factor/Trigger | Respiratory syncitial virus induced wheeze (RSVW) | [173] |
| Asthma and/or wheeze | Factor/Trigger | Viral wheeze | [149] |
| Asthma and/or wheeze | Factor/Trigger | Multiple wheeze | [149] |
| Asthma and/or wheeze | Factor/Trigger | Alternaria-negative asthma | [182] |
| Asthma and/or wheeze | Factor/Trigger | Alternaria-positive asthma | [182] |
| Asthma and/or wheeze | Treatment response | Difficult-to-treat asthma | [187] |
| Asthma and/or wheeze | Treatment response | Steroid sensitive (SS) asthma | [179] |
| Asthma and/or wheeze | Treatment response | Steroid insensitive (SI) asthma | [179] |

# Table S10. Terms used to examine phenotypes in studies assessing comorbidity

|  |  |  |  |
| --- | --- | --- | --- |
| **Allergic disease** | **Group** | **Terms/Phenotypes** | **References** |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Comorbidity | AE + EIA | [141] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Comorbidity | AD and current asthma | [148] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Comorbidity | AD and wheeze | [65] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Comorbidity | Eczema-asthma syndrome | [143] |
| Asthma and/or wheeze;Rhinitis | Comorbidity | Wheezing with rhinoconjunctivitis (RCW);Wheezing wiht rhinitis (RW) | [138] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | comorbidity | Asthma without allergy;Asthma with allergy (hay fever, rhinitis, dermatitis, neurodermatitis) | [63] |
| Food Allergy;Eczema / Atopic Dermatitis | Comorbidity | Food allergy and AE | [45] |
| Food Allergy;Eczema / Atopic Dermatitis | Comorbidity | AD with food hypersensitivity | [39] |
| Food Allergy;Eczema / Atopic Dermatitis | Comorbidity | Transient food allergy + AD; Persistent FA + AD | [66] |
| Food Allergy;Eczema / Atopic Dermatitis | Comorbidity | AD with food hypersensitivity | [39] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | AE | [141] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | AE | [19] |
| Food Allergy;Eczema / Atopic Dermatitis | AE | [45] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Eczema | [122] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Eczema | [114,158,160] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Eczema | [6,18,24,26,32,68,88,126,156] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Eczema | [176] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | AD but no history of asthma | [148] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | AD | [78,125] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | AD | [5,41,83,95,127] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | AD | [115] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | AD | [44,57,86,100] |
| Food Allergy;Eczema / Atopic Dermatitis | AD | [91] |
| Food Allergy;Eczema / Atopic Dermatitis | AD | [39] |
| Food Allergy;Urticaria;Eczema / Atopic Dermatitis | AD | [31] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | AE dermatitis syndrome (AEDS) | [116] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Related term | IgE mediated allergy;Non-IgE mediated allergy | [82] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Related term | Wheeze | [125] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Wheeze | [5,95] |
| Asthma and/or wheeze;Rhinitis | Wheeze | [61] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Wheeze | [6,18,24] |
| Asthma and/or wheeze;Food Allergy | Related term | Asthma | [189] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Asthma | [41,48,122] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Asthma | [114,115,158] |
| Asthma and/or wheeze;Rhinitis | Asthma | [33,107] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Asthma | [18,26,32,42,44,49,68,86,116,126,156] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis | Related term | Bronchial asthma | [87] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Bronchial asthma | [110] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Asthma-like symptoms | [128] |
| Asthma and/or wheeze;FoodAllergy;Eczema / Atopic Dermatitis | Related term | Bronchiolitis | [51] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | BHR | [6,8] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Productive cough | [3] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Lower respiratory tract symptoms (bronchitis; cough; asthma/wheeze) | [1] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Related term | Lower respiratory infection | [176] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Impaired lung function | [89] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Doctor-diagnosed asthma | [95] |
| Asthma and/or wheeze;Rhinitis | Asthma diagnosis | [61] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Diagnosed-asthma | [6] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis | IgE sensitization | Allergic rhinoconjunctivitis | [87] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Allergic rhinoconjunctivitis | [95] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Allergic rhinoconjunctivitis | [115] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Rhinoconjunctivitis | [41] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Rhinoconjunctivitis | [89] |
| Asthma and/or wheeze;Rhinitis | Rhinoconjunctivitis | [107] |
| Asthma and/or wheeze;Rhinitis | IgE sensitization | AR | [33,71,84] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | AR | [122] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | AR | [32,42,44,68,100] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | AR | [102,114] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | AR-like symptoms | [56] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Rhinitis | [5] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Rhinitis | [158] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Rhinitis | [18,24,26,80,116,126,156] |
| Asthma and/or wheeze;Rhinitis | Symptoms with or without temporal pattern | Runny nose | [61] |
| Asthma and/or wheeze;Rhinitis | Symptoms with or without temporal pattern | Diagnosis of hay fever | [61] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Hay fever | [6] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Upper-airway allergy (seasonal or perennial rhinoconjunctivitis) | [128] |
| Asthma and/or wheeze;Rhinitis | Symptoms with or without temporal pattern | Perennial AR | [88] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Seasonal AR | [59] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Dyspnea;Conjunctivitis | [24] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Food hypersensitivity (FH) | [120,122] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Food hypersensitivity (FHS) | [119] |
| Food Allergy;Eczema / Atopic Dermatitis | Food hypersensitivity | [39] |
| Asthma and/or wheeze;Food Allergy | Symptoms with or without temporal pattern | Food allergy | [189] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis | Food allergy | [55,87] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Food allergy | [128] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Food allergy | [114] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Reported diagnosis of food allergy (RDFA) | [120] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Factors/Trigger | Cow's milk allergy | [46,83] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis;Anaphylaxis | Factors/Trigger | Wheat allergy | [191] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis;Anaphylaxis | IgE sensitization | IgE-mediated food allergy | [139] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | IgE sensitization | IgE-mediated CMA; non-IgE-mediated CMA | [50] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Related term | Urticaria | [114,115] |
| Food Allergy;Anaphylaxis | Factors7Trigger | Wheat anaphylaxis | [74] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Oral allergic syndrome | [122] |
| Food Allergy;Urticaria;Eczema / Atopic Dermatitis | Comorbidity | Urticaria without eczema | [31] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | factors/Trigger | Solitary Exercise-induced bronchoconstriction | [106] |
| Asthma and/or wheeze;Rhinitis | Related term | Frequent wheezing (FW) | [138] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | EarlyTransient wheeze | [24] |
| Asthma and/or wheeze;FoodAllergy;Eczema / Atopic Dermatitis | (Early) Transient wheeze | [105,159] |
| Asthma and/or wheeze;FoodAllergy;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Late-onset wheeze | [159] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Late onset wheeze | [24] |
| Asthma and/or wheeze;FoodAllergy;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Persistent wheeze | [105,159] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Persistent wheeze | [3,24] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Recurrent wheeze | [5] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Recurrent Asthma | [142] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Current asthma | [8,89] |
| Asthma and/or wheeze;Rhinitis | Current asthma | [20] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Chronic Asthma | [142] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Chronic persistent asthma | [97] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Persistent asthma | [100] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Current allergic symptoms | [24] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Current rhinoconjunctivitis | [172] |
| Asthma and/or wheeze;Rhinitis | IgE sensitization | Current allergic rhinoconjunctivitis | [20] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Current rhinitis | [136] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Early AD | [65] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Persistent eczema;Intermittenteczema;Transienteczema;Late-onset eczema | [124] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Early onset atopy;Late onset atopy | [6] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Related term | Early childhood atopic;Chronic childhood atopic;Delayed childhood atopic | [167] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Symptoms with or without temporal pattern | Transient FHS;IntermittentFHS;Late onset FHS;Persistent FHS | [120] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Factors/Trigger | Immediate food reactions | [5] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis;Anaphylaxis | Factors/Trigger | Cow milk allergy immediate reactors (to cow milk challenge);Cow milk allergy delayed reactors | [28] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Factors/Trigger | Chronic asthma with Exercise-induced bronchoconstriction;Chronic asthma without Exercise-induced bronchoconstriction;Solitary Exercise-induced bronchoconstriction | [106] |
| Asthma and/or wheeze;Rhinitis | Severity | Mild asthma; Severe asthma | [20] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Mild Asthma;Severe Asthma | [142] |
| Asthma and/or wheeze;Rhinitis | Severity | Mild intermittent asthma | [84] |
| Asthma and/or wheeze;Rhinitis | Severity | Moderate asthma | [20] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Severity | Slight to mild BHR;Moderate to severe BHR | [7] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Severity | Problematic severe asthma;Exacerbations | [97] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Treatment response | Well-controlled asthma | [97] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Eczema / Atopic Dermatitis | Severity | Chronic non-AR;Chronic AR | [101] |
| Asthma and/or wheeze;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Severity | Acute urticaria;Chronicurticaria | [123] |
| Food Allergy;Eczema / Atopic Dermatitis | Severity | Mild AD;ModerateAD;Severe AD | [195] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis | Related term | Atopics;Non-atopics | [111] |
| Asthma and/or wheeze;FoodAllergy;Rhinitis;Urticaria;Eczema / Atopic Dermatitis;Anaphylaxis | Related term | Allergic sensitization (monosensitised,polysensitised) | [132] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Related term | Asymptomatic-sensitized | [19] |
| Asthma and/or wheeze;Rhinitis | IgE sensitization | Atopic wheezing (AW);Non-atopic wheezing (NAW) | [138] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis;Anaphylaxis | IgE sensitization | Rhinits without sensitisation to inhalant allergens;Rhinitis with sensitisation to inhalant allergens | [96] |
| Asthma and/or wheeze;Rhinitis | Related term | Atopy without rhinitis | [71] |
| Asthma and/or wheeze;Rhinitis | Related term | Childhood-onset wheezing | [71] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | Childhood wheeze | [147] |
| Asthma and/or wheeze;Eczema / Atopic Dermatitis | Childhood asthma | [65] |
| Asthma and/or wheeze;Rhinitis;Eczema / Atopic Dermatitis | IgE sensitization | Extrinsic AE; Intrinsic AE | [196] |

# Table S11. Related terms used in already defined phenotypes

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| --- | --- |
| BHR | 72, 92 |
| Cough (current, persistent, late-onset) | 15, 155 |
| Productive cough | 3 |
| Respiratory symptoms | 4, 8, 185 |
| Chest cold | 15 |
| Asthma (current, recurrent, resolved) | 9, 12, 17, 60, 190 |
| Asthma | 14, 18, 26, 27, 32, 33, 41, 42, 43, 44, 47, 48, 49, 68, 72, 75, 86, 90, 93, 107, 108, 113, 114, 115, 116, 122, 126, 127, 134, 144, 145, 156,158,178, 183, 189 |
| Doctor-diagnosed asthma | 4, 6, 12,60, 61, 95, 130,152 |
| Childhood asthma; Infantile asthma | 52,60,65,184 |
| Bronchial asthma | 87, 110 |
| Asthma-like symptoms | 128 |
| Wheeze (history of, current, occasional, frequent, recurrent, past/ex) | 4, 16, 22, 60, 152, 168 |
| Atopics;Non-atopics | 111 |
| Allergic sensitization (monosensitized,polysensitized) | 132 |
| Early onset atopy;Late onset atopy | 6 |
| Early childhood atopic;Chronic childhood atopic;Delayed childhood atopic | 167 |
| Asymptomatic-sensitized | 19 |
| AtopicEczema | 19, 26, 35, 45, 58, 99, 141 |
| Atopic Dermatitis | 5, 31, 34, 38, 39, 41, 44, 57, 78, 79, 83, 86, 91, 95, 100, 115, 125, 127, 148 |
| Atopiceczemadermatitissyndrome | 116 |
| Allergy symptoms | 24 |

# Discussion

Text-mining techniques performed poorly and the same reviewers who screened the titles also screened the first 600 abstracts from excluded studies by means of a table of random numbers to identify those studies that should have been included but that were excluded by title screening. Only two abstracts were found to be clearly eligible for inclusion. Hence, it was concluded that one of the methodological limitations of this systematic review is that around 45 (0.3%) titles rated as excluded should have been included.

Regarding temporal patterns of asthma/wheeze symptoms, the literature has been dominated by the classification and definition of wheezing as early transient, persistent, and late-onset wheeze [177] which has been largely replicated by many but not all studies, in particular cluster analyses [198].

Several triggers have been reported: episodic (viral) and multiple-trigger wheezing phenotypes based on symptom-pattern [21,36,149,169,174], respiratory syncitial virus induced wheeze/bronchiolitis [17,173,182], Alternaria-sensitization in asthma [38] and exercise-induced bronchoconstriction [106].

Many studies assessedIgE sensitization [16,27,30,67,113,133,137,138,151,153,165,178,185]. It has been argued that stratification by atopy in studies of asthma is preferred to a composite definition [199]. Polysensitization has been studied twice[54,81].

Inflammation is an important criterion distinguishing between eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic asthma [15,23,103].

Severity was classified as mild, moderate and severe[2,20,49,84,112,142,149,170,175,187,188,193,194]but also as problematic severe asthma [97] and (severe asthma) exacerbations [97,194].

Treatment response allows to distinguish between steroid-sensitive/resistant asthma [179], difficult-to-treat asthma [64] and well/poorly controlled asthma [97]. However, severity is associated with lack of treatment response and degree of inflammation such as eosinophilic or non-eosinophilic asthma, the latter being characterized by poor response to inhalant corticosteroids associated with impaired asthma control [103], although associations between severity and degree of inflammation (eosinophils) remain controversial [200].

A well-documented hallmark of atopic eczema is its heterogeneity in symptoms, location and timing of symptoms as well as triggers[201]. When studying the temporal pattern of eczema, several phenotypes have been described: early-onset (intermittent), transient, late-onset (intermittent) and persistent eczema [65,70,79,124,164] on one hand and incident, remittent and recurrent eczema [70] on the other. In the search for environmental determinants two phenotypes were distinguished: extrinsic (EAE) and intrinsic atopic eczema (IAE) [196]. However, phenotypes defined by concomitant presence or absence of asthma or wheezing ever explained more heterogeneity of AE than the dichotomization into EAE and IAE. Other studies have used SCORAD to objectively examine disease severity of clinically present eczema[37,64,163,195].

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