Supplementary material to:

Is the association of early day care attendance with childhood asthma explained by underlying susceptibility?

Aino K. Rantala,[a,b,c] Maria C. Magnus,[d,e,f] Øystein Karlstad,[a] Hein Stigum,[a] Siri E. Håberg,[d] Per Nafstad,[a,g] Wenche Nystad,[a#] Jouni J.K. Jaakkola[b#]

[a]Division of Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway, [b]Center for Environmental and Respiratory Health Research, University of Oulu, Oulu, Finland, [c]Medical Research Center Oulu, Oulu, Finland, [d]Centre for Fertility, Norwegian Institute of Public Health, Oslo, Norway, [e]MRC Integrative Epidemiology Unit at the University of Bristol, Bristol, United Kingdom, [f]Population Health Science, Bristol Medical School, Bristol, United Kingdom, [g]Department of Community Medicine, University of Oslo, Oslo, Norway

[#] These authors contributed equally to this work.

Corresponding author: Aino K Rantala, Center for Environmental and Respiratory Health Research, P.O.Box 5000, FI-90014 University of Oulu, Finland. E-mail: aino.rantala@oulu.fi

eAppendix 1: Stata code for forming of the disease risk score and analyses of effect modification of the association between early day care attendance and risk of asthma in both Complete Case Data and Multiple Imputed Data sets

```
***********************************************************************************
Full-cohort disease risk score (DRS)
***********************************************************************************
**********************Complete Case Data*****************************************

logistic ID_AlleRx_proxy_6_30_365_mm day_care_b18m atopic_derm_6m asthma_6m lrti_6m mother_asthma
mother_atopy ptb daily_smoking mother_edu bmi_2 cs parity mother_age gender

*prediction of the risk of asthma when the exposure is set unexposed
gen day_care_b18m_org = day_care_b18m
replace day_care_b18m = 0 if day_care_b18m <.
predict DRSf0
replace day_care_b18m =day_care_b18m_org

**********************Multiple Imputed Data***********************************

*prediction is not possible for mi estimation so DRS has to be estimated in a loop for every mi set
gen day_care_b18m_org=day_care_b18m_m
forvalues m=1(1)$M        {
        logistic ID_AlleRx_proxy_6_30_365_mm day_care_b18m_m atopic_derm_6m_m asthma_6m_m
        lrti_6m_m mother_asthma mother_atopy_noasthma ptb daily_smoking mom_edu bmi_2 cs parity
        MORS_ALDER kjonn if _mi_m==`m'
        cap drop DRSf0`m'
        replace day_care_b18m_m=0 if day_care_b18m_m<.
        predict DRSf0`m' if _mi_m==`m'
        replace day_care_b18m_m=day_care_b18m_org
}

gen DRSf0_mi=0 if _mi_m!=0
forvalues m=1(1)$M        {
        replace DRSf0_mi=DRSf0`m' if (_mi_m==`m')
}

***********************************************************************************
Figure 3 - Plotting the association between day care and DRS under interaction between them
***********************************************************************************
**********************Complete Case Data*****************************************

* Change scale and form rounded DRS values for plotting
gen DRSf0_100=(DRSf0*100)
gen DRSI=round(DRSf0_100)

*Spline function of DRS
mkspline sp4=DRSf0, cubic knots(.0221417 .0347128 .0840843  0.2) display

*Poisson logistic model
glm ID_AlleRx_proxy_6_30_365_mm day_care_b18m##c. sp4?, fam(poisson) link(log) eform vce(robust)
margins, over(DRSI) at(day_care_b18m=(0 1)) post coeflegend
```

```
*RR with CLs from margins
input x rr lci uci
end

* Loop over the margins result, use nlcom to calculate RR with CI
local bn bn
foreach j of numlist 1(1) 45 47 48 50 51 52 53 54 55 56 58 59 60 61 62 63 64 68 69 75 77{
        qui nlcom log( _b[2._at#`j'`bn'.DRSI]/_b[1bn._at#`j'`bn'.DRSI])         //log(RR)
        local bn ""
        mat b=r(b)
        qui replace rr=exp(b[1,1]) in `j'              //RR
        mat V=r(V)
        local se=sqrt(V[1,1])
        qui replace lci=exp(b[1,1]-1.96*`se') in `j'    // Lower CI
        qui replace uci=exp(b[1,1]+1.96*`se') in `j'   // Upper CI
}
replace x=_n if rr<.
list rr lci uci if rr<.

* Plot of RR with CI by x
tw (rarea lci uci x, col(gs10%30))(line rr x, con(asc)) ///
, yscale(log) leg(off) yline(1, lcol(red)) ytitle("RR")  xlabel(3"0.03" 10"0.10" 20"0.20" 30"0.30" 40"0.40" 50"0.50"
60"0.60" 70"0.70" 76"0.76") xtitle("Disease Risk Score (DRS)")

*******************Multiple Imputation Data*****************************************
* Change scale and form rounded DRS values for plotting
gen DRSf0_100=(DRSf0_mi*100)
gen DRSI=round(DRSf0_100)

*Spline function of DRS
mkspline sp4=DRSf0_mi if _mi_m!=0, cubic knots(.02204 .0344665 .083309  0.2) display

* Poisson logistic model with mi estimation
mi estimate: glm ID_AlleRx_proxy_6_30_365_mm day_care_b18m_m##c.sp4?, fam(poisson) link(log) eform
vce(robust)

* margins for each mi dataset using mimrgns command
mimrgns, over(DRSI) at(day_care_b18m_m=(0 1))  predict(default)  post coeflegend


*RR with CLs from margins
input x rr lci uci
end

* Loop over the margins result, use nlcom to calculate RR with CI
local bn bn
foreach j of numlist 1(1)52 54 55 56 59 60 61 63 65 68 70 76{
        qui nlcom log( _b[2._at#`j'`bn'.DRSI]/_b[1bn._at#`j'`bn'.DRSI])              // log(RR)
        local bn ""
        mat b=r(b)
        qui replace rr=exp(b[1,1]) in `j'                                            // RR
        mat V=r(V)
```

```
            local se=sqrt(V[1,1])
            qui replace lci=exp(b[1,1]-1.96*`se') in `j'                          // Lower CI
            qui replace uci=exp(b[1,1]+1.96*`se') in `j'                          // Upper CI
}
replace x=_n if rr<.
list rr lci uci if rr<.


* Compute required data for box plot of DRS:
gen maxY=5
egen med_DRSI=median(DRSI)
egen upq_DRSI = pctile(DRSI),p(75)
egen loq_DRSI = pctile(DRSI),p(25)
egen mean_DRSI=mean(DRSI)
egen iqr_DRSI=iqr(DRSI)
egen upper_DRSI=max(min(DRSI,upq_DRSI+1.5*iqr_DRSI))
egen lower_DRSI = min(max(DRSI,loq_DRSI-1.5*iqr_DRSI))


* Plot of RR with CI by x and box plot for distribution of DRS levels in the same figure
tw (rarea lci uci x, col(gs10%30))(line rr x, con(asc))   ///   Plot of RR with CI
(rbar med_DRSI upq_DRSI maxY, blc(navy) bfc(white) barw(1.5) hor) /// Box plot of DRSI
(rbar med_DRSI loq_DRSI maxY, blc(navy) bfc(white) barw(1.5) hor) ///
(rspike upq_DRSI upper_DRSI maxY , blc(navy) hor) ///
(rspike loq_DRSI lower_DRSI maxY , blc(navy) hor) ///
(rcap upper_DRSI upper_DRSI maxY , blc(navy) msize(*1) hor) ///
(rcap lower_DRSI lower_DRSI maxY , blc(navy) msize(*1) hor) ///
(scatter maxY mean_DRSI , pstyle(p1) ms(dh) msize(*1) mls(*.8) mlc(navy%20) ) /// Diamond for mean
(scatter maxY DRSI if !inrange(DRSI, lower_DRSI, upper_DRSI), ms(oh) mc(navy%20) legend(off)) /// Outliers
, yscale(log) leg(off) yline(1, lcol(red)) ytitle("RR")  xlabel(3"0.03" 10"0.10" 20"0.20" 30"0.30" 40"0.40" 50"0.50"
60"0.60" 70"0.70" 76"0.76") xtitle("Disease Risk Score (DRS)")
```

eTable 1. Akaike and Bayesian information criterions (AIC and BIC) comparing the fit of multiplicative and additive models using linear or cubic splines of disease risk score (DRS) (n=50,478).

Function of DRS in the model	Model with multiplicative scale		Model with additive scale	
	AIC	BIC	AIC	BIC
Linear	16803	16839	16326	16361
Cupic spline with 3 knots[a]	16523	16576	16324	16377
Cupic spline with 4 knots[b]	16503	16574	16328	16398
Cupic spline with 4 knots[c]	16484	16554	16326	16396
Cupic spline with 5 knots[d]	16482	16570	16323	16411

[a] 0.022; 0.034; 0.083
[b] 0.020; 0.030; 0.041; 0.107
[c] 0.022; 0.034; 0.083; 0.20
[d] 0.022; 0.034; 0.083; 0.20; 0.40

Results

eTable 2. Means of covariates according to the percentiles of the disease risk score (DRS).

|	DRS < 1st	1st ≤ DRS < 5th	5th ≤ DRS < 10th	10th ≤ DRS < 25th	25th ≤ DRS < 50th	50th ≤ DRS < 75th	75th ≤ DRS < 90th	90th ≤ DRS < 95th	95th ≤ DRS < 99th	99th ≤ DRS
	DRS < 0.018	0.018 ≤ DRS < 0.020	0.020 ≤ DRS < 0.022	0.022 ≤ DRS < 0.027	0.027 ≤ DRS < 0.034	0.034 ≤ DRS < 0.050	0.050 ≤ DRS < 0.083	0.083 ≤ DRS < 0.107	0.107 ≤ DRS < 0.209	0.209 ≤ DRS
Child characteristics										
Sex (1=boy, 2= girl)	2	2	1.986	1.839	1.465	1.263	1.399	1.214	1.219	1.197
LRTI at 6 months (0/1)	0	0	0.002	0.010	0.023	0.058	0.082	0.075	0.167	0.319
Atopic dermatitis at 6 months (0/1)	0	0	0	0	0.001	0.030	0.384	0.597	0.547	0.752
Asthma like symptoms at 6 months (0/1)	0	0	0	0	0	0	0.002	0.022	0.157	0.575
Born preterm (0/1)	0	0	0.0004	0.002	0.017	0.061	0.111	0.070	0.124	0.114
Caesarean section (0/1)	0	0.001	0.008	0.039	0.079	0.193	0.237	0.194	0.303	0.301
Maternal characteristics										
Mothers age (cont)	32.30	30.96	30.28	30.32	30.20	30.09	30.17	29.81	29.85	29.87
BMI (cont)	20.66	21.43	22.25	22.91	23.52	24.80	25.04	24.99	26.52	27.08
Maternal asthma (0/1)	0	0	0	0	0	0.007	0.191	0.333	0.473	0.643
Maternal atopy (0/1)	0	0.007	0.018	0.138	0.236	0.406	0.454	0.624	0.689	0.676
Maternal smoking: stopped smoking by 18 gestational weeks (0/1)	0.012	0.041	0.074	0.124	0.131	0.167	0.154	0.149	0.178	0.162
Maternal smoking during whole pregnancy (0/1)	0	0.004	0.016	0.056	0.075	0.131	0.121	0.125	0.171	0.168
Maternal education: Less than secondary school (0/1)	0	0	0.001	0.006	0.032	0.051	0.100	0.093	0.139	0.146
Secondary school (0/1)	0.11	0.051	0.131	0.267	0.275	0.365	0.347	0.361	0.405	0.423
Up to 4 years of university (0/1)	0.182	0.407	0.582	0.430	0.469	0.387	0.382	0.410	0.349	0.323
More than 4 year of university (0/1)	0.806	0.542	0.281	0.272	0.206	0.149	0.171	0.136	0.107	0.108
Number of siblings (parity)	1.960	1.200	0.930	0.900	0.780	0.660	0.710	0.660	0.710	0.830

BMI, body mass index; LRTI, lower respiratory tract infection

eTable 3. Risk ratios (RR) and risk differences (RD) for asthma with 95% confidence intervals for early day care attendance in interaction with disease risk score using multiplicative and additive models, respectively (n=55,404).

Disease risk score	RR of asthma (95% CI)	RD of asthma (95% CI)
0.01	0.90 (0.66, 1.23)	0.001 (-0.007, 0.009)
0.02	0.88 (0.72, 1.10)	-0.001 (-0.006, 0.004)
0.03	0.87 (0.76, 0.99)	-0.004 (-0.007,-0.0003)
0.04	0.85 (0.75, 0.95)	-0.007 (-0.012, -0.002)
0.05	0.83 (0.72, 0.95)	-0.010 (-0.016, -0.004)
0.06	0.82 (0.71, 0.94)	-0.014 (-0.020, -0.007)
0.07	0.81 (0.71, 0.91)	-0.017 (-0.025, -0.008)
0.08	0.80 (0.71, 0.90)	-0.019 (-0.030, -0.008)
0.09	0.79 (0.70, 0.90)	-0.021 (-0.035, -0.007)
0.10	0.79 (0.69, 0.91)	-0.022 (-0.038, -0.006)
0.11	0.79 (0.69, 0.92)	-0.022 (-0.040, -0.005)
0.12	0.80 (0.68, 0.94)	-0.022 (-0.041, -0.004)
0.13	0.80 (0.68, 0.95)	-0.021 (-0.041, -0.002)
0.14	0.81 (0.68, 0.97)	-0.020 (-0.041, -0.001)
0.15	0.82 (0.68, 0.98)	-0.019 (-0.040, 0.002)
0.16	0.83 (0.69, 1.00)	-0.017 (-0.039, 0.005)
0.17	0.84 (0.70, 1.01)	-0.015 (-0.038, 0.009)
0.18	0.86 (0.72, 1.02)	-0.012 (-0.037, 0.013)
0.19	0.87 (0.73, 1.04)	-0.010 (-0.037, 0.017)
0.20	0.88 (0.74, 1.05)	-0.007 (-0.037, 0.022)
0.21	0.90 (0.75, 1.07)	-0.005 (-0.037, 0.028)
0.22	0.91 (0.77, 1.09)	-0.002 (-0.037, 0.033)
0.23	0.93 (0.78, 1.11)	0.001 (-0.038, 0.039)
0.24	0.94 (0.79, 1.13)	0.003 (-0.039, 0.045)
0.25	0.96 (0.80, 1.15)	0.006 (-0.040, 0.051)
0.26	0.97 (0.81, 1.17)	0.008 (-0.040, 0.056)
0.27	0.99 (0.82, 1.20)	0.011 (-0.041, 0.063)
0.28	1.01 (0.83, 1.23)	0.013 (-0.042, 0.069)
0.29	1.02 (0.83, 1.26)	0.016 (-0.043, 0.075)
0.30	1.04 (0.84, 1.28)	0.018 (-0.044, 0.081)
0.31	1.06 (0.85, 1.32)	0.021 (-0.046, 0.088)
0.32	1.07 (0.85, 1.35)	0.024 (-0.047, 0.094)
0.33	1.09 (0.86, 1.39)	0.026 (-0.049, 0.100)
0.34	1.11 (0.87, 1.42)	0.029 (-0.049, 0.106)
0.35	1.13 (0.87, 1.46)	0.031 (-0.050, 0.113)
0.36	1.15 (0.88, 1.50)	0.034 (-0.052, 0.120)
0.37	1.17 (0.88, 1.54)	0.036 (-0.053, 0.125)
0.38	1.19 (0.89, 1.59)	0.039 (-0.054, 0.132)
0.39	1.20 (0.90, 1.63)	0.041 (-0.055, 0.138)
0.40	1.23 (0.90, 1.68)	0.044 (-0.056, 0.145)
0.41	1.24 (0.90, 1.72)	0.047 (-0.058, 0.151)
0.42	1.27 (0.90, 1.78)	0.050 (-0.059, 0.159)
0.43	1.28 (0.91, 1.82)	0.052 (-0.060, 0.170)
0.44	1.31 (0.91, 1.87)	0.054 (-0.061, 0.170)
0.45	1.33 (0.92, 1.93)	0.057 (-0.063, 0.177)

|		
0.46	1.35 (0.92, 1.98)	0.060 (-0.064, 0.183)
0.47	1.37 (0.92, 2.04)	0.062 (-0.065, 0.189)
0.48	1.39 (0.93, 2.09)	0.064 (-0.066, 0.194)
0.49	1.41 (0.93, 2.16)	0.067 (-0.068, 0.202)
0.50	1.44 (0.93, 2.23)	0.070 (-0.069, 0.209)
0.51	1.46 (0.94, 2.29)	0.072 (-0.070, 0.215)
0.52-0.53	1.49 (0.94, 2.37)	0.075 (-0.072, 0.223)
0.54	1.54 (0.95, 2.51)	0.080 (-0.075, 0.235)
0.55	1.56 (0.95, 2.57)	0.082 (-0.075, 0.240)
0.56-0.58	1.60 (0.95, 2.68)	0.086 (-0.077, 0.250)
0.59	1.67 (0.96, 2.91)	0.093 (-0.081, 0.268)
0.60	1.69 (0.96, 2.97)	0.095 (-0.082, 0.272)
0.61-0.62	1.73 (0.97, 3.08)	0.098 (-0.084, 0.280)
0.63-0.64	1.79 (0.97, 3.28)	0.104 (-0.086, 0.294)
0.65-0.67	1.85 (0.98, 3.49)	0.109 (-0.089, 0.308)
0.68-0.69	1.95 (0.99, 3.84)	0.118 (-0.093, 0.329)
0.70-0.75	2.10 (1.00, 4.42)	0.129 (-0.100, 0.359)
0.76-0.77	2.23 (1.01, 4.92)	0.139 (-0.104, 0.382)

The disease risk scores are rounded so that, for example, 0.02 includes DRSs between 0.015 and 0.024.
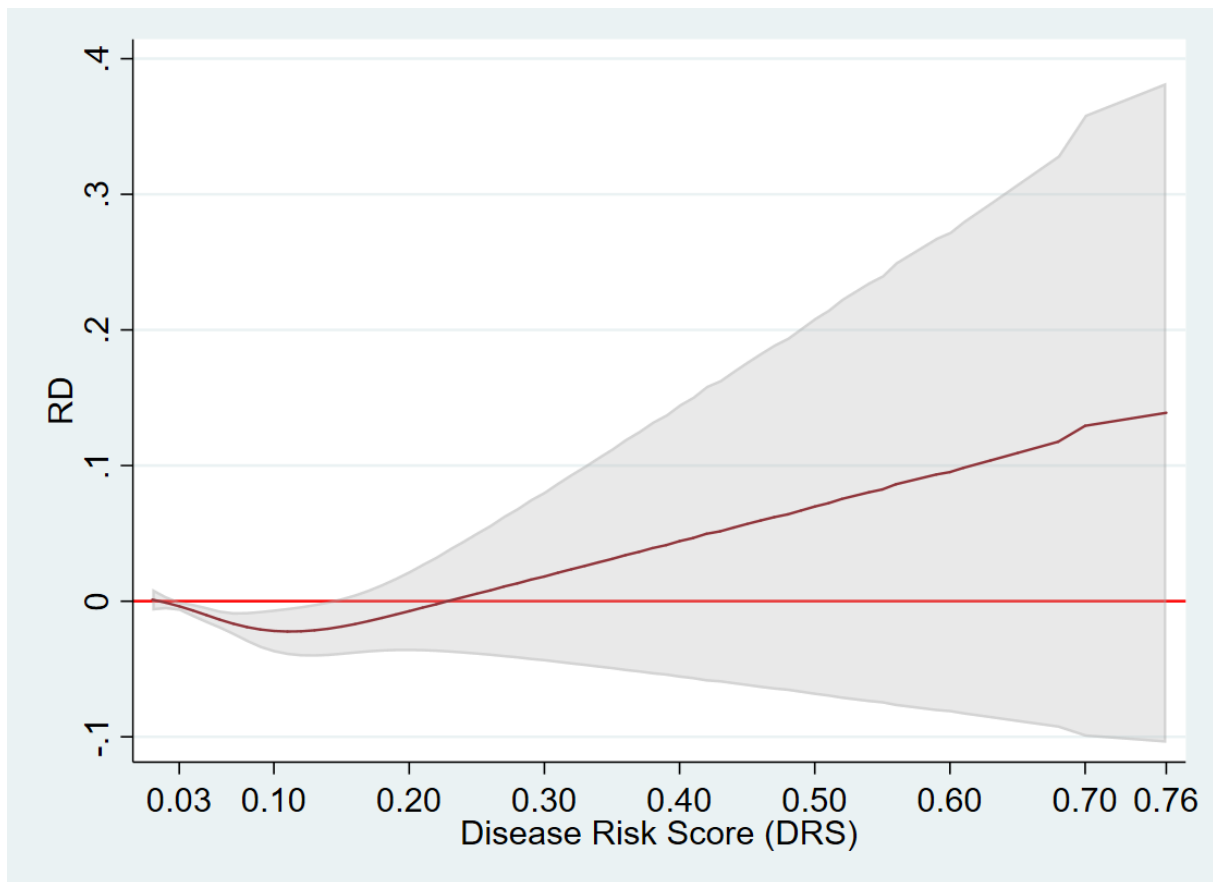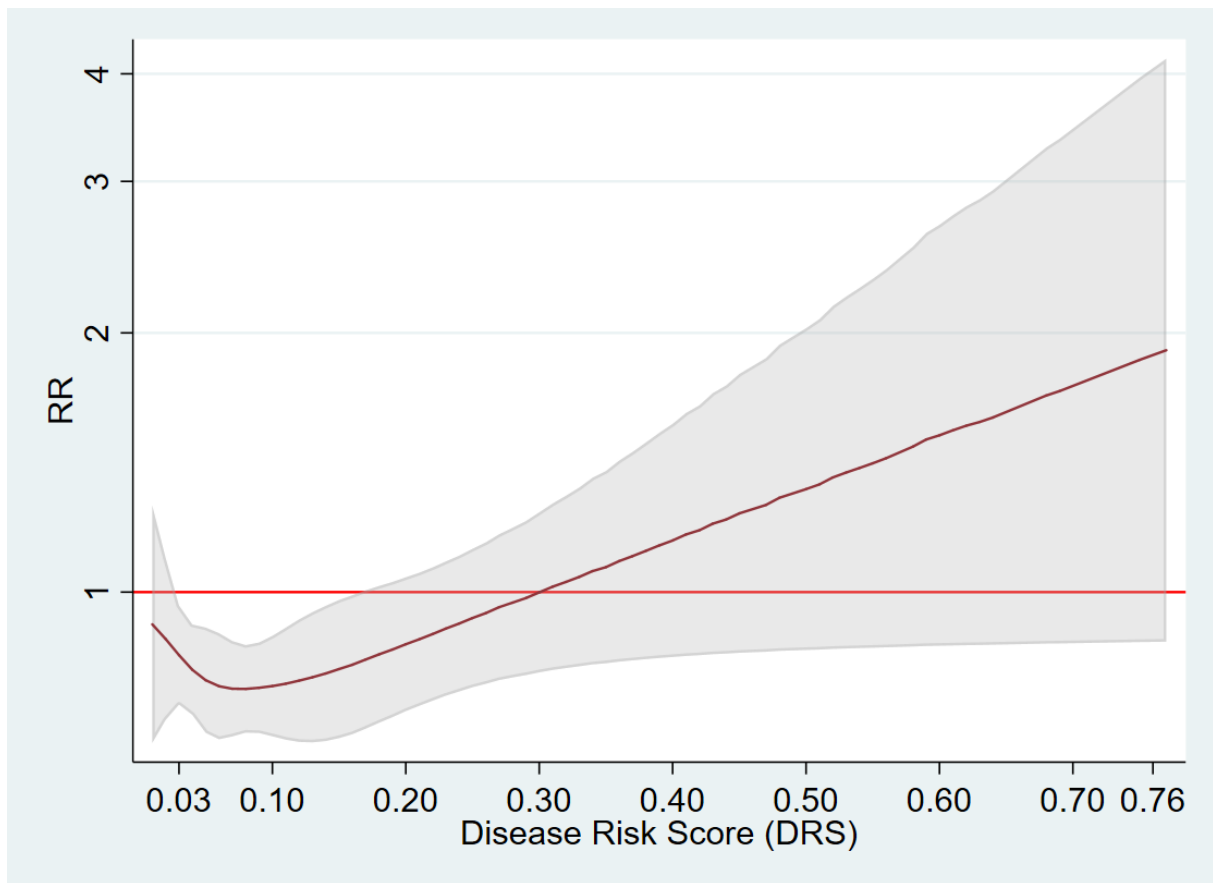
eFigure 1. The effect of early day care attendance on the risk of asthma measured as risk difference (RD) (y-axis) at different levels of Disease Risk Score (x-axis) (n=55,404). The shaded area shows the 95% confidence intervals. The smoothed curve presents the RD's against DRS levels at intervals of 0.01.
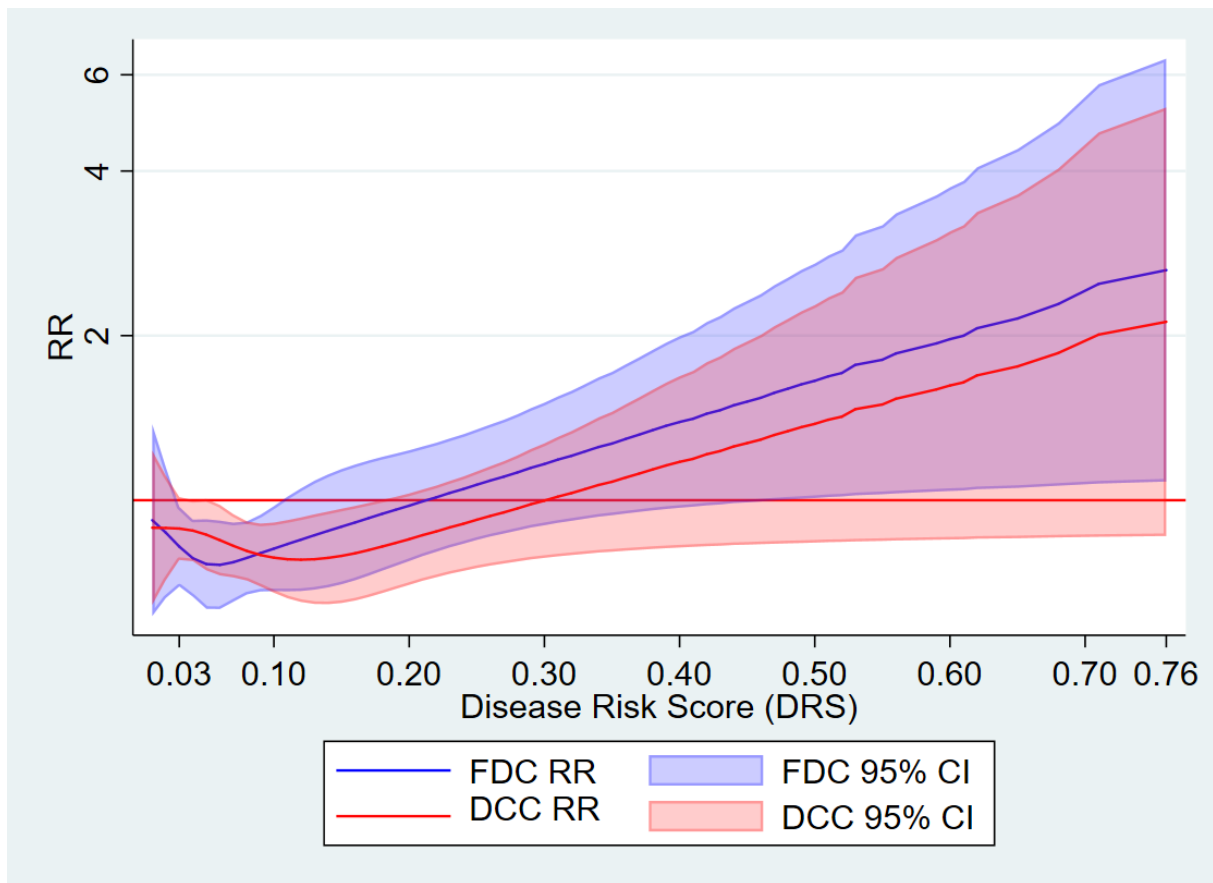
eFigure 2. Risk ratios for asthma with 95% confidence intervals for family day care (FDC) (blue) or day care center (DCC) (red), in interaction with DRS (n=55,404).
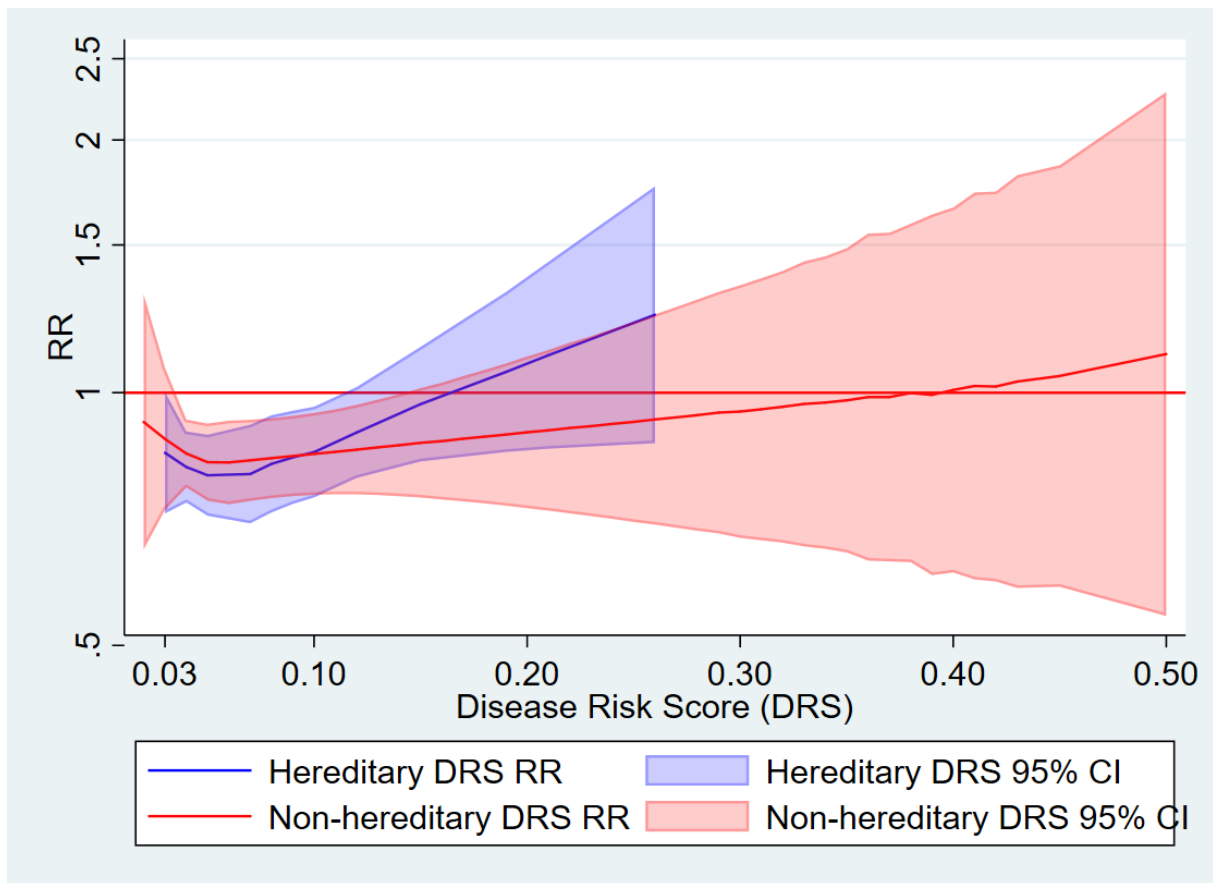
eFigure 3. Risk ratios for asthma with 95% confidence intervals for early day care attendance in interaction with hereditary (blue) and non-hereditary (red) DRS (n=55,404)

eFigure 4. The effect of early day care attendance on the risk of asthma measured as risk ratio (RR) (y-axis) at different levels of Disease Risk Score (x-axis) in the complete case data (n=50,487). The shaded area shows the 95% confidence intervals. The smoothed curve presents the RR's against DRS levels at intervals of 0.01.
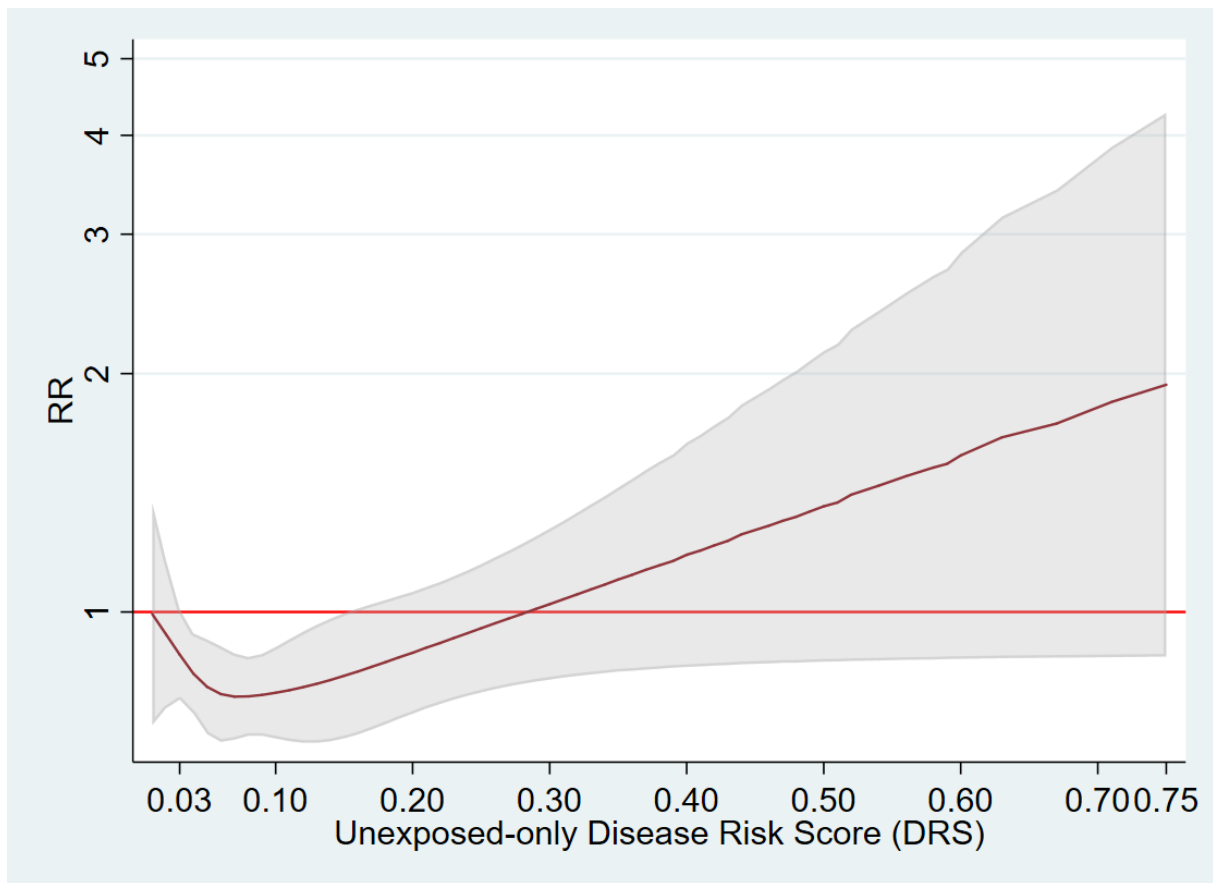
eFigure 5. The effect of early day care attendance on the risk of asthma measured as risk ratio (RR) (y-axis) at different levels of "unexposed-only" Disease Risk Score (x-axis) (n=55,404). The shaded area shows the 95% confidence intervals. The smoothed curve presents the RR's against DRS levels at intervals of 0.01.