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# Is the Association of Early Day Care Attendance with Childhood Asthma Explained by Underlying Susceptibility?

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**Background:** Previous studies of early day care attendance and asthma development are inconsistent, which may be explained by inadequate control of confounding and effect modification. We examined the effect of early day care on the risk of asthma taking into account the underlying susceptibility to asthma.

**Methods:** The study included 55,404 children participating in the Norwegian Mother, Father and Child Cohort Study. Asthma at age 7 was defined by dispensed asthma medications in the Norwegian Prescription Database. We defined a disease risk score (DRS) to account for an underlying susceptibility to asthma including a range of hereditary and nonhereditary predictors of asthma. We assessed confounding and modifying effects of DRS on the association between day care and asthma.

**Results:** Day care before 18 months was associated with a lower risk of asthma by age 7 (adjusted risk ratio [RR] = 0.85; 95% confidence interval [CI] = 0.78, 0.92) when compared with home care. DRS modified the estimated effect of day care on asthma risk. Among the 80% of children with DRS between 0.03 and 0.16, day care was associated with a reduced asthma risk (RRs between 0.79 and 0.87), whereas among 0.5% of children with a high DRS (above 0.28), estimated effect of day care on asthma increased gradually (RR for the highest DRS 2.2; 1.0–4.9).

**Conclusions:** In our study, among most children, early day care was associated with reduced asthma risk at 7 years, and increased risk in a small group of children with very high underlying susceptibility to asthma.

**Keywords:** Asthma; Disease risk score; Early day care; MoBa; The Norwegian Mother, Father and Child Cohort Study

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The consents and approvals for MoBa do not allow storage of data in repositories. However, it is possible to apply for access to datasets for replication from datatilgang@fhi.no. Ethical approval and relevant agreements will be required. Statistical code is available in eAppendix; http://links.lww.com/EDE/B635.

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Asthma is the most common chronic disease among children.[1] There is accumulating evidence that genetic predisposition and environmental exposures in early childhood influence the risk of asthma later in life,[2–5] although the underlying causal mechanisms remain unclear. Both early respiratory tract infections and day care attendance have been associated with higher risk of developing asthma.[6–11] Children attending day care are exposed to several environmental factors that are likely to influence the development of asthma.[12–15] However, previous studies of early day care attendance and asthma development have inconsistent results, and report protective effect against asthma,[16,17] increased risk of asthma,[8,18–21] conflicting effect,[22,23] or no effect.[24] One explanation for these inconsistencies is that the studies are not comparable due to methodologic differences, such as inadequate or varying control for confounding and effect modification. A few studies have controlled for maternal asthma or

atopy when estimating the association between day care and asthma risk, but their findings were conflicting.[23,24] Several characteristics of the parents and the child (such as early life respiratory symptoms) may influence the timing and probability of day care attendance and at the same time be associated with asthma or influence the potential effect of day care on the risk of asthma.

Previous studies of day care attendance and risk of asthma may differ because they have used more traditional statistical methods without elaboration of effect modifiers. There is a need to address this research question by taking into account that the relationship between day care attendance and the risk of asthma might be explained by confounding and effect modification, that is, underlying susceptibility to the effects of day care environment.

The objective of the present study was to assess the effect of early day care attendance on the risk of asthma at the age of 7 years taking into account (1) confounding and (2) the modifying effect of underlying susceptibility to asthma. We used data from The Norwegian Mother, Father and Child Cohort Study (MoBa), which includes information from more than 114,000 children since pregnancy, and with linkage to the Norwegian Prescription Database (NorPD) there was near complete follow-up of the cohort to age 8.[25,26]

## METHODS

### Study Population

MoBa is a prospective population-based cohort that includes more than 114,000 children and their parents. Women were recruited at approximately 18 weeks of gestation between 1999 and 2008.[25,26] The participation rate was 41%. All participants gave written informed consent. We included all children in MoBa who were singletons, still alive and living in Norway, with information from the Medical Birth Registry of Norway, who had reached 8 years at the time of linkage to the NorPD (July 2015) and had information from the 6-month and 18-month questionnaires (Figure 1). This left 55,404 children in the analysis. The establishment and data collection in MoBa was previously based on a license from the Norwegian Data Inspectorate and approval from The Regional Committee for Medical Research Ethics, and it is now based on regulations related to the Norwegian Health Registry Act.

### Childhood Asthma

The definition of asthma was based on dispensed asthma medications from the Norwegian Prescription Database (NorPD). Asthma at age 7 was defined as having at least two dispensed prescription for asthma medications: one in the 12 months preceding the seventh birthday, in addition to a second dispensed prescription within 12 months after the first. Asthma medications included inhaled beta(2)-agonists (R03AC), inhaled glucocorticoids (R03BA), combinations of inhaled beta(2)-agonists and glucocorticoids (R03AK), and leukotriene receptor antagonists (R03DC).

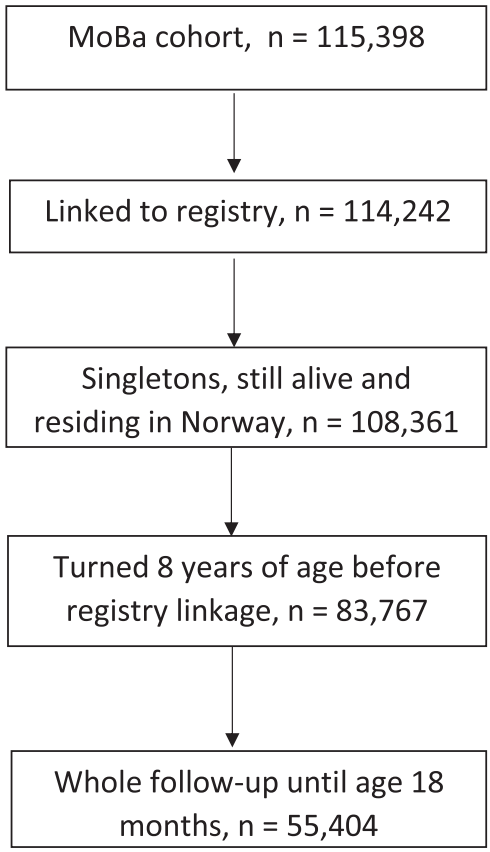


**FIGURE 1.** Selection of the study population.

### Daycare Attendance

We obtained information on day care attendance when the child was 6 and 18 months old from questionnaires.[27] The mother was asked where and how her child was cared for during the day when he/she was 0–6 months, 7–9 months, 10–12 months, 13–15 months, and 16–18 months. The list of alternative response categories included "at home with a parent" and "at home with a childminder," which we categorized as home care, and "at a childminder's/in a family day nursery" and "in a day care center," which were categorized as family day care and day care center, respectively. In the analyses, any period in a family day care or day care center before 18 months of age (occasional or regular attendance) was regarded as early attendance at day care. Most Norwegian children start their day care between 1 and 2 years of age depending on the parents' choice. Therefore, it is likely that the choice is partly based on maternal and early childhood characteristics, which are potentially related to asthma and health in general.

### Disease Risk Score

We included all child and maternal characteristics which we assumed were determinants of both early day care attendance and the development of asthma and used these to define a disease risk score (DRS) for asthma.[28,29] This DRS was then used as a summary measure for confounding variables and it was also used to explore effect modification. Figure 2

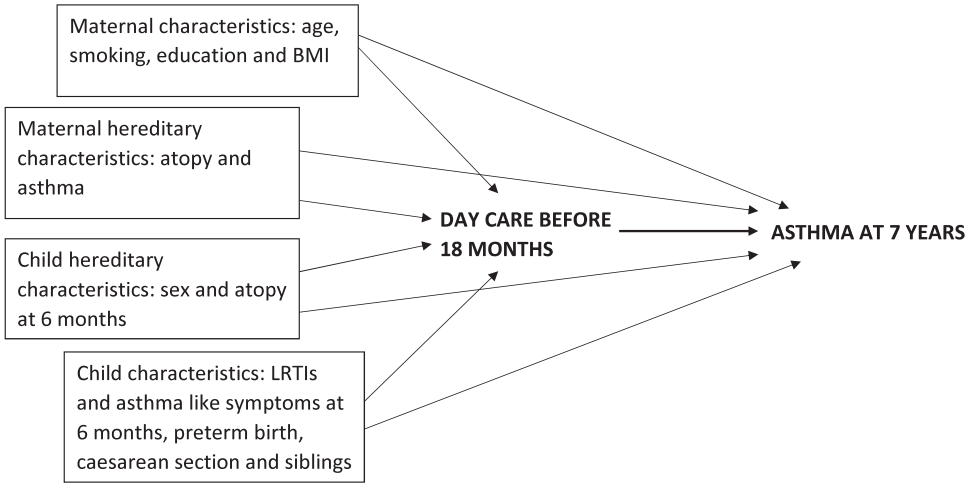


**FIGURE 2.** Causal diagram for capturing factors that we have included in the DRS describing underlying susceptibility to asthma. BMI, body mass index; LRTI, lower respiratory tract infections.

shows the causal diagram of our selection of covariates included in the DRS in order to describe underlying susceptibility to asthma. Maternal characteristics included were age at delivery, body mass index (BMI), history of asthma, history of atopy, smoking during pregnancy, and educational level. Child characteristics were obtained from the Medical Birth Registry and included sex, preterm birth, delivery by cesarean section, and number of siblings. From MoBa questionnaires at age 6 months, we included early childhood information on occurrence of lower respiratory tract infections (LRTIs) and presence of atopic dermatitis and asthma-like symptoms (Figure 2).

The DRS is an estimate of the probability of disease occurrence as a function of the exposure and covariates setting exposure to zero. We applied a full-cohort DRS, which is the multivariate confounder score originally proposed by Miettinen Olli.[28] The DRS score was estimated from the full cohort using a logistic regression model with asthma as the outcome and the exposure (day care) and all the covariates included in the model. The risk of asthma was then predicted from this model using the individual covariates for each study subject while setting the exposure status as unexposed (see Stata code in eAppendix 1; http://links.lww.com/EDE/B635). This DRS has a value reflecting the predicted probability of asthma for each child and ranges between 0 and 1.

We conducted sensitivity analysis for the main results using an unexposed-only DRS model to avoid modeling heterogeneity in the effect of the exposure when fitting the risk model. We estimated the unexposed-only DRS in a sample of unexposed from a logistic regression model of asthma as an outcome and all the covariates included in the model. The risk of asthma was then predicted from this model for all the study subjects. To avoid the overfitting of DRS, we used a random unexposed sample (n = 5,000) for estimation with 100 repetitions.[30]

## Statistical Analyses

We compared the distribution of child and maternal characteristics in children who attended day care with children who were still in home care before age of 18 months. We assessed the differences in the distribution of covariates according to the day care attendance using chi-square tests for the categorized variables and analysis of variance (ANOVA) for the continuous variables.

We assessed the relationship between day care attendance and asthma at 7 years by comparing the risk of asthma among children who attended day care with the risk among children in home care before age of 18 months. The risk ratios (RRs) of asthma and 95% confidence intervals (CIs) were estimated using Poisson regression models with robust variance estimation. We analyzed the impact of the DRS on the effect estimates between early day care attendance and asthma in two ways. First, we adjusted for the DRS in the multivariable model. Second, we assessed the modifying effect of the DRS and plotted the RR for the relation between day care attendance and the risk of asthma after including an interaction term between day care and the DRS. The smoothed plot presents the RR's at different levels of DRS at intervals of 0.01. We tested linearity of the interaction between DRS and day care using splines and a model with a spline function of DRS was found to be best based on the Akaike information criterion (see eTable 1; http://links.lww.com/EDE/B635 for the model fit statistics). We were able to obtain the model fit statistics only in the complete case data. We applied four knots, of which three were based on proportion distribution and one included among the highest values of DRS (DRS 0.20). We used a multiplicative scale in our analysis, but have included results in an absolute scale in the online supplementary material; http://links.lww.com/EDE/B635.

In addition to the DRS which summarized all the potential covariates, we created a separate DRS for hereditary

asthma risk based on maternal history of asthma or atopy and infant gender and history of atopic dermatitis. Nonhereditary asthma risk was based on lifestyle and environmental characteristics (Figure 2).

Altogether, 7% of the children in the study population had missing information on at least one of the covariates. We imputed the missing values (from N = 51,788 to N = 55,404) using chained equations (seven imputations) and present the results from the multiple imputed data set. We also present main results from the complete case data set. The imputation model included the exposure and the outcome, all covariates with missing information, as well as the following variables without missing information (sex, delivery by cesarean section, number of siblings, maternal age, and asthma at 7 years). We conducted the analyses in Stata version 15 (StataCorp, College Station, TX).[31]

## RESULTS

In total, 69% of the children attended day care (48% attended day care centers and 21% family day care), and 31% were still in home care at age 18 months. Table 1 shows the distributions of child and maternal characteristics according to day care attendance. Children who attended day care were less likely to have LRTIs, asthma-like symptoms, or atopic dermatitis at age 6 months; fewer siblings; and were less frequently born preterm or delivered by cesarean section than children who were cared for at home. Mothers of children attending day care were less frequently smokers, had less asthma, more frequently reported atopy, and had higher education level compared to mothers whose children were cared for at home (Table 1). BMI of the mothers whose children attended day care was lower (23.9 kg/m$^2$) than BMI of the mothers whose children were cared for at home before 18 months (24.2 kg/m$^2$). These findings were in concordance with the underlying theoretical framework (Figure 2).

The prevalence of asthma at the age of 7 years was 4.2%. Any day care attendance before 18 months was associated with a decreased risk of asthma at 7 years. Altogether 3.9% of children who attended day care and 4.8% of the children with no day care before 18 months had asthma at age 7 (crude RR = 0.80; 95% CI = 0.74, 0.87). Adjustment for the DRS only slightly attenuated the observed association, with an adjusted RR of 0.85 (95% CI = 0.78, 0.92) and an adjusted risk difference (RD) of –0.005 (95% CI = –0.008, –0.002). Adjustment for the individual variables instead of the DRS produced a similar effect estimate (adjusted RR = 0.85; 95% CI = 0.78, 0.93).

The average asthma DRS was 0.05 (corresponding to the overall prevalence of asthma) (SD 0.04), where the lowest and highest DRS were 0.01 and 0.77, respectively. eTable 2; http://links.lww.com/EDE/B635 in online supplementary material describes the means of the covariates according to the percentiles of DRS.

The DRS modified the association of early day care attendance with risk of asthma. This was evidenced by an interaction between the DRS score and early day care on the risk of asthma (test of interaction $P$ = 0.087). Figure 3 shows the association of day care attendance with risk of asthma as RRs at different levels of the DRS. When the DRS was low (≤0.02), representing 18% of the children, early day care had no association or a negative association with asthma risk. However, among the majority of the children (80%) who had a DRS between 0.03 and 0.16, early day care was associated with a reduced risk of asthma (RRs between 0.79 and 0.87) (Figure 3 and eTable 3; http://links.lww.com/EDE/B635). When the DRS was higher (≥0.28), representing about 0.5% of the children, the association of early day care attendance with asthma increased gradually. At the extreme tail of the DRS distribution, early day care showed a higher risk of asthma, with an adjusted RR of 2.2 (95% CI = 1.0, 4.9) (Figure 3). The effect modification was also present when using an additive scale (test of interaction $P$ = 0.034) (eFigure 1; http://links.lww.com/EDE/B635). eTable 3; http://links.lww.com/EDE/B635 shows all the RRs and RDs with their 95% CI at different levels of the DRS. The DRS was a modifier of the association of day care with the risk of asthma for attendance at both types of day care, family day care, and day care center (eFigure 2; http://links.lww.com/EDE/B635).

We compared the influence of hereditary and nonhereditary DRS separately and observed an interaction between early day care and hereditary DRS on the risk of asthma ($P$ = 0.094), while there was no such interaction between early day care and nonhereditary DRS ($P$ = 0.702). eFigure 3; http://links.lww.com/EDE/B635 shows the association with early day care attendance in interaction with hereditary and nonhereditary DRS on the risk of asthma.

We conducted several sensitivity analysis of the main findings. First, we analyzed all the models among those with complete data and the results were similar. Early day care attendance was associated with a risk of asthma at 7 years with an adjusted RR of 0.83 (95% CI = 0.76, 0.91). In eFigure 4; http://links.lww.com/EDE/B635, the effect of day care attendance on the risk of asthma as RR at different levels of DRS in the complete case data is present. Second, we used models with unexposed-only DRS and the results remained similar. In the multiple imputed data, mean unexposed-only DRS was 0.05 (SD 0.04) and the lowest and highest DRS were 0.01 and 0.76, respectively. Early day care attendance was associated with a risk of asthma at 7 years with an adjusted RR of 0.85 (95% CI = 0.78, 0.92). eFigure 5; http://links.lww.com/EDE/B635 shows the effect of day care attendance on the risk of asthma at different levels of unexposed-only DRS.

## DISCUSSION

In our large population-based study, early day care attendance was associated with a decreased risk of asthma at age 7. However, an underlying susceptibility to asthma seemed to modify the effect of day care on the risk of asthma. Among the most susceptible children (<0.5%), who had the highest asthma DRS, early day care was associated with an increased risk of asthma.

**TABLE 1.** Distribution of Child and Maternal Characteristics by Day Care Attendance Before 18 Months of Age (n = 55,404[a])

| Characteristic | Home Care by 18 Months, n (%) | Day Care by 18 Months, n (%) |
|---|---|---|
| | 17,198 (31) | 38,206 (69) |
| Gender | | |
| Boy | 8,868 (52) | 19,472 (51) |
| Girl | 8,330 (48) | 18,734 (49) |
| LRTI (≥1) at 6 months | | |
| No | 16,249 (95) | 36,488 (96) |
| Yes | 949 (5.5) | 1,718 (4.5) |
| Atopic dermatitis at 6 months | | |
| No | 15,016 (87) | 33,491 (88) |
| Yes | 2,182 (13) | 4,715 (12) |
| Asthma-like symptoms at 6 months | | |
| No | 16,938 (99) | 37,725 (99) |
| Yes | 260 (1.5) | 481 (1.3) |
| Born preterm (<37 weeks) | | |
| No | 16,335 (95) | 36,521 (96) |
| Yes | 863 (5.0) | 1,685 (4.4) |
| Delivered by cesarean section | | |
| No | 14,812 (86) | 33,152 (87) |
| Yes | 2,386 (14) | 5,054 (13) |
| Number of siblings | | |
| 0 | 6,426 (37) | 18,714 (49) |
| 1 | 5,653 (33) | 13,799 (36) |
| 2 | 3,735 (22) | 4,733 (12) |
| 3 or more | 1,384 (8.0) | 960 (2.5) |
| Maternal age at delivery (years) | | |
| <25 | 2,320 (14) | 3,247 (8.5) |
| 25–29 | 5,585 (33) | 13,165 (34) |
| 30–34 | 6,113 (36) | 15,642 (41) |
| 35+ | 3,180 (19) | 6,152 (16) |
| Maternal asthma | | |
| No | 15,924 (93) | 35,480 (93) |
| Yes | 1,274 (7.4) | 2,726 (7.1) |
| Maternal atopy | | |
| No | 11,996 (70) | 25,896 (68) |
| Yes | 5,202 (30) | 12,310 (32) |
| Maternal smoking at start of pregnancy | | |
| No | 12,701 (74) | 29,898 (78) |
| Stopped by 18 gestational weeks | 2,346 (14) | 5,290 (14) |
| Continued after 18 gestational weeks | 2,151 (13) | 3,018 (7.9) |
| Maternal education | | |
| Less than secondary school | 2,166 (13) | 1,667 (4.4) |
| Secondary school | 6,726 (39) | 9,834 (26) |
| Up to 4 years of university | 6,195 (36) | 17,126 (45) |
| More than 4 year of university | 2,111 (12) | 9,579 (25) |

[a]Analyses performed in the imputed dataset. Rounded average cell counts and percentages are shown based on results from imputed data.

## Validity of the Results

This MoBa study of 55,404 children provided information on a large number of potential confounders of the association between day care and asthma development. We formed a DRS for asthma to summarize a set of important potential confounders, following the approach by Miettinen Olli[28] forming a multivariate confounder score. There are several advantages with using a DRS compared to using separate individual confounder variables. First, control for confounding by adjusting the multivariate regression model for the DRS results in a more parsimonious model. Second, a summary score provides a single numeric measure for characterizing disease risk. This is useful in the assessment of both nonlinear exposure–outcome functions and when assessing effect modification. We found that the DRS might modify the effect of early day care on the risk of asthma. In the most parsimonious model, the RR for the relation between day care attendance and asthma was first decreased from DRS values 0.01 to 0.27 and then increased monotonously according to DRS variables up to 0.77. Arbogast Patrick and Ray Wayne[29] have studied the performance of the DRS, derived from either full cohort or only unexposed population, by comparing it with the more commonly used propensity score, which is a probability of being exposed as a function of observed covariates, and with traditional multivariable outcome regression. Their finding was that all models performed well, but that the full-cohort DRS emerged as a useful tool for cohort studies to directly estimate each cohort member's risk of developing the study outcome, particularly when assessing effect modification.[29] However, there are inconsistent findings on potential bias of using unexposed-only and full-cohort DRS methods.[32] We elaborated whether DRS modifies the effect of early day care on the risk of asthma also using an "unexposed-only" DRS as a sensitivity analysis and found that the association of day care with asthma development was similar compared to the analysis using full-cohort DRS.

We found similar effect modification by DRS on the association between day care and asthma using multiplicative and additive scales. However, there was a difference in the precision of the increased risk of asthma with high DRS levels. It is important to be aware that early day care attendance was associated with increased risk of asthma in the multiplicative scale only among less than 0.5% of the children. Therefore, this finding requires a very cautious interpretation from a public health perspective, and we emphasize that a protective effect of day care on asthma was found in a majority of children, both in multiplicative and additive scale. On the other hand, if the estimated 2.2-fold increased effect of day care on asthma among children with high underlying susceptibility is true, it would have an important public health impact for this highly susceptible subgroup.

One limitation of the study is that some of the underlying susceptibility to asthma may be explained by unmeasured baseline characteristics not included in the DRS. For

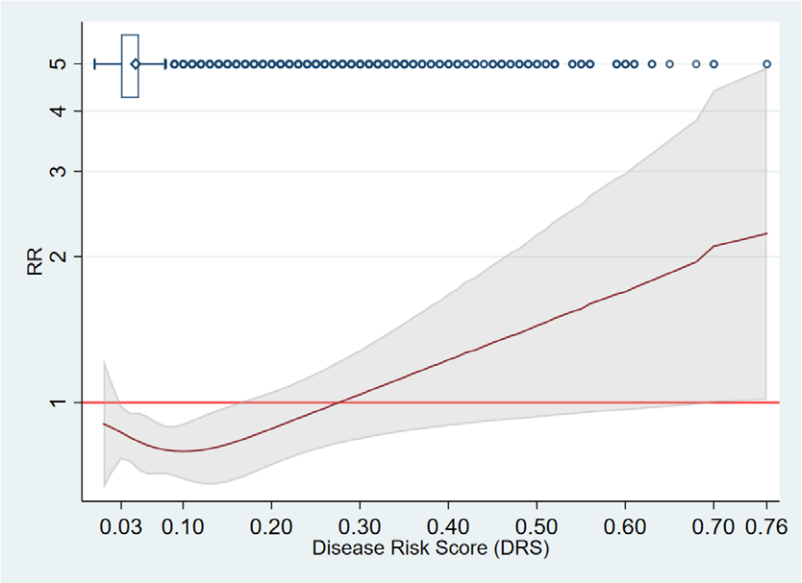


**FIGURE 3.** The effect of early day care attendance on the risk of asthma measured as RR (*y*-axis) at different levels of DRS (*x*-axis) (n = 55,404). The shaded area shows the 95% CIs. The smoothed curve presents the RR's against DRS levels at intervals of 0.01. DRS-specific RR's are given in eTable 3; http://links.lww.com/EDE/B635. A box plot for the distribution of DRS levels is shown above the figure.

example, genetic predisposition to asthma. We did not have a genetic data available in this study, but did include maternal asthma and atopy as a proxy for genetic risk. We included the available determinants of day care and asthma as potential confounders that were measured before 6 months of age in the DRS, as only 0.2% of the children attended family day care or day care center before age of 6 months. However, it is likely that the choice of day care attendance was partly based on the early childhood characteristics.

The participation rate in MoBa was 41%, which could introduce some selection bias. However, it has been shown that differences between the characteristics of MoBa study population and all Norwegian mothers giving birth in the same time period did not introduce any bias for studied perinatal exposure–outcome relationships.[33] We were able to minimize loss to follow-up selection bias by having a complete follow-up at 7 years for all who turned 8 years old before registry linkage, which was used to define asthma. However, we had to exclude 34 % of the children because of missing information from the 6 or 18 months questionnaires. The selection was primarily seen for according to maternal age, parity, and smoking, but prevalence of maternal and offspring asthma was similar. There is convincing evidence that dispensed asthma medication (yes vs. no) is an excellent indicator of the presence of asthma among 7 years old Norwegian children.[34]

## Synthesis with Previous Knowledge

Findings from the previous studies on early day care attendance and asthma development have been inconsistent.[8,16–24,35,36] Differences in these findings may be explained by inadequate control of individual susceptibility as well as differences in practice of the age of day care attendance and differences in assessment of onset of asthma. Studies reporting inverse association between early day care and asthma have considered the risk of asthma mainly in children at school age,[16,17,23,35,36] consistent with our results. In a prospective cohort study of 453 children, maternal history of asthma modified the relation between day care and childhood asthma.[23] In that study, day care during the first year of life decreased the risk of asthma by 6 years of age only among children who did not have mother with asthma, whereas among children of mothers with asthma, day care was associated with increased risk of asthma.[23] Our findings are in line with their results as we found an increasing risk of asthma among children with increasing hereditary DRS. However, we were also able to take into account several early risk factors for asthma, including maternal asthma and atopy, as well as environmental and lifestyle exposures, to form a DRS, and we found that the effect of early day care on later asthma was modified by the underlying susceptibility to asthma.

Previous studies showing a positive relation between day care and the risk of asthma have mostly included preschool-aged children.[8,18–21] We also investigated the association between day care and parental reported asthma at age of 3 years, and we found a similar positive association. However, it is likely that asthma during preschool age is a mix of real asthma and other respiratory-related symptoms. Previous studies have suggested that most of the asthma in early childhood, a phenotype called transient early wheezing, resolves before age 3 years.[37]

## Interpretation of the Results

Almost all Norwegian children spend their first year in home care, because of a long paid parental leave. In this study population, only 14% of the children started day care before 12 months of age. Parents also have the option to stay at home with the child and receive a childcare benefit payment when the child is between 1 and 2 years of age. Therefore, parents can choose when their child starts in day care. It is likely that the choice is partly based on maternal and early

childhood characteristics, which may be related to asthma and health in general. We observed that maternal and early childhood characteristics did influence the frequency of early day care attendance. Although known determinants of asthma, such as lower respiratory tract infections and atopic dermatitis were less common in children who attended day care at an early age, selection into day care did not explain the finding that early day care attendance reduced the risk of developing asthma by the age of 7. This might be partly explained by the finding that lower number of siblings, which is known to be associated with increased risk of asthma, was more common in children who attended day care. Similar day care policies are applied in other Nordic countries, but in most of the other countries like United States that lack paid parental leave, the educational status of the mother or family dominates the decision. Therefore, selection into day care may vary between study populations and explain inconsistent study results.

The mechanisms that could explain the inverse association between early day care and the risk of asthma are not clear. Previously, the increased occurrence of respiratory infections in children attending day care has been used to explain both the increasing and decreasing associations of day care attendance with risk of asthma,[8,17,18,21] and day care has been used as a proxy measure of frequent infections. However, accumulating evidence by us and others has shown that respiratory infections are more likely to be associated with increased risk of asthma.[7,9,11,38] In contrast, it has been suggested that exposure to other children at home or at day care during the early childhood is protective against asthma.[35] Diversity of microbial contacts during infancy (which may be more likely in day care settings) may be favorable for the microbiota maturation and stability and thereby might contribute to reduced risk of allergic diseases.[39] Results of the current study suggests that associations of day care with risk of asthma may be modified by an underlying predisposition to asthma. This may explain the observed conflicting findings of the relation between day care attendance and the risk of asthma in previous studies.

## CONCLUSIONS

In our study, early day care attendance was associated with reduced risk of asthma. Only in a small group of children (<0.5%), with the highest underlying susceptibility to asthma, was early day care associated with increased risk of later asthma.

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