



Universiteit
Leiden
The Netherlands

No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth

Baas, E.M.; Romijn, M.; Pal, S.M. van der; Vrijlandt, E.J.L.E.; Rotteveel, J.; Finken, M.J.J.; ...
; Dutch POPS 19 Col

Citation

Baas, E. M., Romijn, M., Pal, S. M. van der, Vrijlandt, E. J. L. E., Rotteveel, J., Finken, M. J. J., ... Steenbrugge, G. J. van. (2021). No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth, 73(1), 226-229. doi:10.1007/s12020-021-02672-7

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3575901>

Note: To cite this publication please use the final published version (if applicable).

University of Groningen

No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth

Dutch POPS 19 Col; Baas, Emma M.; Romijn, Michelle; van der Pal, Sylvia M.; Vrijlandt, E. J. L. E.; Rotteveel, Joost; Finken, M. J. J.

Published in:
Endocrine

DOI:
[10.1007/s12020-021-02672-7](https://doi.org/10.1007/s12020-021-02672-7)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Dutch POPS 19 Col, Baas, E. M., Romijn, M., van der Pal, S. M., Vrijlandt, E. J. L. E., Rotteveel, J., & Finken, M. J. J. (2021). No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth. *Endocrine*, 73(1), 226-229. <https://doi.org/10.1007/s12020-021-02672-7>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.


Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth

Emma M. Baas¹ · Michelle Romijn¹  · Sylvia M. van der Pal² · Elianne J. L. E. Vrijlandt³ · Joost Rotteveel¹ · Martijn J. J. Finken¹ · Dutch POPS-19 Collaborative Study Group

Received: 10 July 2020 / Accepted: 24 February 2021 / Published online: 20 March 2021
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

In preterm infants in their first weeks of life, the hypothalamic-pituitary-adrenal (HPA) axis is unable to produce sufficient amounts of cortisol for the degree of illness [1, 2]. The causes for this phenomenon are prolonged central suppression, immature adrenocortical enzymes and a cortisol-cortisone shuttle that favors cortisone [1, 3]. Cortisol is known for its anti-inflammatory effect. It has been demonstrated among preterm infants that low-cortisol levels may predispose to disrupted lung development, manifested as bronchopulmonary dysplasia (BPD) in approximately 20% of all infants born <32 weeks of gestation [4, 5].

A factor that might contribute to lung development after preterm birth is sensitivity to glucocorticoids. In adults, single-nucleotide polymorphisms (SNPs) in the glucocorticoid receptor (GR) gene have previously been associated with alterations in glucocorticoid sensitivity [6, 7]. The R23K polymorphism has been associated with decreased sensitivity to glucocorticoids [8], while the N363S polymorphism has been associated with increased glucocorticoid sensitivity [9].

We hypothesized that GR polymorphisms, might influence respiratory morbidity after preterm birth. Previous

studies among preterm infants showed that these GR polymorphisms were not associated with the risk of developing BPD [10, 11]. However, the consequences of GR polymorphisms on long-term respiratory outcome after very preterm birth remain to be explored. Therefore, we investigated associations between the GR polymorphisms R23K and N363S and long-term respiratory outcomes in a cohort of subjects born very preterm birth who were followed up until young adulthood.

Materials and methods

Study design and participants

For this study, data from the Project On Preterm and Small-for-gestational-age infants (POPS) study were used. The POPS study is a birth cohort study that had included 94% ($N = 1338$) of all liveborn very preterm (i.e., gestational age <32 weeks) and/or very-low-birth-weight (i.e., <1500 grams) infants throughout the Netherlands in 1983. Various perinatal and neonatal characteristics were collected from birth onwards, including the presence of BPD. BPD was defined as clinical signs of respiratory distress in conjunction with abnormal findings on a chest X-ray and supplemental oxygen at 28 days of age [5]. At the age of 19 years, all alive subjects were approached to participate in a follow-up study (POPS-19 study), in which, among other data, GR polymorphisms were collected. The study was approved by the medical ethics committee of all participating centers. All subjects gave written informed consent for participation in this study [8].

Data collection

Respiratory outcomes were determined by self-report using the European Community Respiratory Health Survey (ECRHS) questionnaire [12]. The ECRHS questionnaire

These authors contributed equally: Emma M. Baas, Michelle Romijn

Members of the Dutch POPS-19 Collaborative Study Group are listed below Author contributions.

✉ Michelle Romijn
m.romijn1@amsterdamumc.nl

¹ Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Endocrinology, Amsterdam, The Netherlands

² TNO, Child Health, Leiden, The Netherlands

³ Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Department of Pediatric Pulmonology and Pediatric Allergy, Groningen, The Netherlands

Table 1 Respiratory outcomes at age 19 and neonatal respiratory outcomes by genotype

	Genotype			OR + 95% CI		P value	
	R23K N = 21	N363S N = 15	Non-carriers N = 258	R23K vs non-carriers	N363S vs non-carriers	R23K vs non-carriers	N363S vs non-carriers
Respiratory outcomes at age 19							
Eczema— <i>n</i> (%)	5 (23.8%)	1 (6.7%)	24 (9.3%)	3.05 (1.03, 9.05)	0.70 (0.09, 5.53)	0.045	0.73
Hay fever— <i>n</i> (%)	1 (4.8%)	3 (20.0%)	18 (7.0%)	0.67 (0.09, 5.26)	3.33 (0.86, 12.89)	0.70	0.08
Asthma— <i>n</i> (%)	1 (4.8%)	1 (6.7%)	19 (7.4%)	0.68 (0.09, 5.36)	1.02 (0.13, 8.25)	0.71	0.99
Asthma attack last 12 months— <i>n</i> (%)	1 (4.8%)	0 (0.0%)	5 (1.9%)	NA	NA	1.00	1.00
Chest wheezing last 12 months— <i>n</i> (%)	8 (38.1%)	3 (20.0%)	56 (21.7%)	2.19 (0.86, 5.54)	0.89 (0.24, 3.29)	0.10	0.86
SOB during exercise— <i>n</i> (%)	4 (19.0%)	0 (0.0%)	34 (13.2%)	1.28 (0.40, 4.06)	NA	0.68	1.00
SOB while walking with people same age— <i>n</i> (%)	1 (4.8%)	0 (0.0%)	12 (4.7%)	0.86 (0.11, 6.98)	NA	0.89	1.00
Need to stop for breath when walking at own pace on level ground— <i>n</i> (%)	0 (0.0%)	0 (0.0%)	8 (3.1%)	NA	NA	1.00	1.00
Neonatal respiratory outcomes							
BPD— <i>n</i> (%)	1 (4.8%)	2 (13.3%)	20 (7.8%)	0.60 (0.08, 4.67)	1.83 (0.39, 8.69)	0.62	0.45
CPAP or IPPV, days—median [IQR]	3 [0–11]	1 [0, 6]	2 [0, 8]	1.03 (0.98, 1.07)	1.02 (0.97, 1.07)	0.23	0.40

SOB shortness of breath, BPD bronchopulmonary dysplasia, CPAP continuous positive airway pressure, IPPV Intermittent positive pressure ventilation, N number, IQR interquartile range

was developed from pre-existing questionnaires that had already been used in multinational studies [12–14], and contains questions about the presence of respiratory problems or symptoms. Symptoms on the ECRHS questionnaire showed correlation with objective measures of lung function [15]. This questionnaire was sent to all subjects known to be alive. At the same time, subjects were seen for blood sampling at one of the participating centers [8].

Laboratory analysis

GR SNPs were determined by performing polymerase chain reactions using 2.5 ng of genomic DNA and standard reagents. Subsequently, they were genotyped by mass spectrometry using standard conditions [8]. The genotype distribution for both the R23K and the N363S polymorphism was in agreement with the distribution predicted by the Hardy–Weinberg equilibrium ($P = 0.54$ for the R23K polymorphism, and $P = 0.66$ for the N363S polymorphism), and are mutual exclusives.

Statistical analysis

Statistical analyses were performed with SPSS Statistics version 26. Patient characteristics were compared between R23K carriers and non-carriers, and between N363S carriers and non-carriers, using the Chi square-test for dichotomous data and the independent samples *t*-test or their nonparametric equivalents for continuous data. Outcomes were compared between R23K carriers and non-carriers, and between N363S carriers and non-carriers, using logistic regression analysis.

Results

Of the 1012 very preterm born infants 676 (67%) were still alive at the age of 19. Of these, 498 (74%) consented to participate in the POPS-19 study. In 318 (64%) of them genomic data and ECHRS symptoms were known. After the exclusion of subjects with any congenital malformation, 294 were available for analysis, including 21 (7%) R23K carriers, 15 (5%) N363S carriers and 258 (88%) non-carriers.

Perinatal characteristics did not differ between the groups (data not shown).

Respiratory outcomes at age 19 are shown by GR genotype in Table 1. No differences in scores of asthma, chest wheezing or shortness of breath were found between R23K carriers and non-carriers, or between N363S carriers and non-carriers. Eczema was positively associated with R23K carriage (OR 3.05, 95% CI 1.03, 9.05, p value 0.045).

Furthermore, no differences in the duration of respiratory support with continuous positive airway pressure (CPAP), intermittent positive pressure ventilation (IPPV) or the numbers developing BPD were seen between R23K carriers and non-carriers and N363S carriers and non-carriers.

Discussion

In this study we found no association between the GR polymorphisms R23K and N363S and respiratory outcomes 19 years after very preterm birth.

Respiratory outcome after preterm birth is determined by a complex interplay of lung immaturity, need for and duration of assisted ventilation, oxygen supplies, and recurrent or enduring infections [16], in addition to other factors that are not specifically related to prematurity, such as socioeconomic status, (maternal) smoking, BMI, and physical activity [17]. Furthermore, our sample was born in the pre-surfactant era [18]. Increasing degrees of prematurity and BPD were associated with more airflow impairment later in life [17], possibly due to the presence of smaller airways [19, 20]. Although GR SNPs might influence some of these processes, due to the multitude of factors that determine respiratory outcome after preterm birth their overall contribution is probably negligible.

We found that carriers of the R23K polymorphism had a higher odds of eczema. Although this association might reflect a biologically plausible mechanism, it could also be a chance finding. However, contrary to expectation, we found that carriers of the N363S polymorphism had a higher odds of hay fever. Clearly, our results should be balanced against the small numbers of variant allele carriers.

We found GR polymorphisms to be unrelated to the odds of BPD, consistent with findings by Schreiner et al. [10]. The lack of association can be explained by the complex multifactorial pathophysiology of BPD or by selective survival of certain genotypes [21]. However, the genotype frequencies in this study did not differ from the genotype frequencies in the Dutch norm population, which argues against a major survivor effect [8].

Our study has several strengths, including a large sample size and long-term follow-up. Our study also has its limitations. Even though this study had a relatively large sample size, the number of variant allele carriers ($n = 36$) was small. Nonetheless, the genotype distribution for both polymorphisms was in agreement with the distribution predicted by the Hardy–Weinberg equilibrium. Second, the POPS-19 study was not designed specifically for our research question. GR SNPs were determined at age 19. In the early 1980s, many very preterm infants did not survive, which inevitably may

give rise to selection bias. In addition, participants were not representative for the current generation of very preterm infants, which are more immature. Insufficient cortisol production and BPD are more frequent at lower gestational ages [2]. Third, patient-reported respiratory data are not as objective as data derived from spirometry. Since respiratory problems may develop many years after preterm birth, serial follow-up of spirometry would allow to determine the course of pulmonary development after very preterm birth. Fourth, our study lacked an assessment of adrenocortical output and inflammatory markers during the neonatal course.

In summary, our study did not show associations between the GR polymorphisms R23K and N363S and long-term respiratory outcome 19 years after very preterm birth. Future studies on this topic should include serial measurements of adrenocortical output along with inflammatory markers during the neonatal course, and should include an objective assessment of lung function.

Authors' contributions E.M.B., M.R., S.M.P., E.J.L.E.V., J.R., M.J.J.F. made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; drafted the work or revised it critically for important intellectual content; approved the version to be published; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Dutch POPS-19 Collaborative Study Group E. T. M. Hille⁴, C. H. de Groot⁴, H. Kloosterboer-Boerrigter⁴, A. L. den Ouden⁴, A. Rijpstra⁴, S. P. Verloove-Vanhorick⁴, J. A. Vogelaar⁴, J. H. Kok⁵, A. Ilsen⁵, M. van der Lans⁵, W. J. C. Boelen-van der Loo⁵, T. Lundqvist⁵, H. S. A. Heymans⁵, E. J. Duiverman⁶, W. B. Geven⁶, M. L. Duiverman⁶, L. I. Geven⁶, E. J. L. E. Vrijlandt⁶, A. L. M. Mulder⁷, A. Gerver⁷, L. A. A. Kollée⁸, L. Reijmers⁸, R. Sonnemans⁸, J. M. Wit⁹, F. W. Dekker⁹, M. J. J. Finken⁹, N. Weisglas-Kuperus¹⁰, M. G. Keijzer-Veen¹⁰, A. J. van der Heijden¹⁰, J. B. van Goudoever¹⁰, M. M. van Weissenbruch¹¹, A. Cranendonk¹¹, H. A. Delemarre-van de Waal¹¹, L. de Groot¹¹, J. F. Samsom¹¹, L. S. de Vries¹², K. J. Rademaker¹², E. Moerman¹², M. Voogseerd¹², M. J. K. de Kleine¹³, P. Andriessen¹³, C. C. M. Dielissen-van Helvoirt¹³, I. Mohamed¹³, H. L. M. van Straaten¹⁴, W. Baerts¹⁴, G. W. Veneklaas Slots-Kloosterboer¹⁴, E. M. J. Tuller-Pikkemaat¹⁴, M. H. Ens-Dokkum¹⁵, G. J. van Steenbrugge¹⁶

⁴TNO Quality of Life, Leiden, The Netherlands; ⁵Emma Children's Hospital AMC, Amsterdam, The Netherlands; ⁶University Hospital Groningen, Beatrix Children's Hospital, Groningen, The Netherlands; ⁷University Hospital Maastricht, Maastricht, The Netherlands; ⁸University Medical Center St Radboud, Nijmegen, The Netherlands; ⁹Leiden University Medical Center, Leiden, The Netherlands; ¹⁰Erasmus MC – Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands; ¹¹V.U. University Medical Center, Amsterdam, The Netherlands; ¹²Wilhelmina Children's Hospital, UMC, Utrecht, The Netherlands; ¹³Máxima Medical Center, Veldhoven, The Netherlands; ¹⁴Isala Clinics, Zwolle, The Netherlands; ¹⁵Royal Effatha Guyot Group, Zoetermeer, The Netherlands; ¹⁶Dutch Association of Parents of Newborn Infants, Leidschendam, The Netherlands

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

- M.J. Finken et al. Glucocorticoid programming in very preterm birth. *Horm. Res. Paediatr.* **85**(4), 221–231 (2016)
- K.L. Watterberg, S.M. Scott, Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. *Pediatrics* **95**(1), 120–125 (1995)
- M.J.J. Finken et al. Programming of the hypothalamus-pituitary-adrenal axis by very preterm birth. *Ann. Nutr. Metab.* **70**(3), 170–174 (2017)
- K.L. Watterberg et al. Links between early adrenal function and respiratory outcome in preterm infants: airway inflammation and patent ductus arteriosus. *Pediatrics* **105**(2), 320–324 (2000)
- E. Bancalari et al. Bronchopulmonary dysplasia: clinical presentation. *J. Pediatr.* **95**(5 Pt 2), 819–823 (1979)
- K. Ogasawara et al. A polymorphism in the glucocorticoid receptor gene is associated with refractory hypotension in premature infants. *Pediatr. Neonatol.* **59**(3), 251–257 (2018)
- D.M. Haas et al. The impact of glucocorticoid polymorphisms on markers of neonatal respiratory disease after antenatal beta-methasone administration. *Am. J. Obstet. Gynecol.* **208**(3), 215 e1–215216 (2013)
- M.J. Finken et al. The 23K variant of the R23K polymorphism in the glucocorticoid receptor gene protects against postnatal growth failure and insulin resistance after preterm birth. *J. Clin. Endocrinol. Metab.* **92**(12), 4777–4782 (2007)
- N.A. Huizenga et al. A polymorphism in the glucocorticoid receptor gene may be associated with and increased sensitivity to glucocorticoids in vivo. *J. Clin. Endocrinol. Metab.* **83**(1), 144–151 (1998)
- C. Schreiner et al. Glucocorticoid receptor gene variants and neonatal outcome in very-low-birth-weight preterm infants. *Neonatology* **111**(1), 22–29 (2017)
- R. Bertalan et al. Association between birth weight in preterm neonates and the BclI polymorphism of the glucocorticoid receptor gene. *J. Steroid Biochem. Mol. Biol.* **111**(1–2), 91–94 (2008)
- E.J. Vrijlandt et al. Gender differences in respiratory symptoms in 19-year-old adults born preterm. *Respir. Res.* **6**, 117 (2005)
- G. Biino et al. ECRHS screening questionnaire scoring: a methodological suggestion for asthma assessment. *European Community Health Survey. J. Outcome Meas.* **4**(4), 740–762 (2000)
- P.G. Burney et al. The European Community Respiratory Health Survey. *Eur. Respir. J.* **7**(5), 954–960 (1994)
- H.M. Boezen et al. Relation between respiratory symptoms, pulmonary function and peak flow variability in adults. *Thorax* **50**(2), 121–126 (1995)
- E.J. Vrijlandt et al. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. *J. Pediatr.* **150**(3), 256–261 (2007)
- P. Nasanen-Gilmore et al. Lung function in adults born preterm. *PLoS ONE* **13**(10), e0205979 (2018)
- N. El-Gendy et al. Delivery and performance of surfactant replacement therapies to treat pulmonary disorders. *Ther Deliv* **4**(8), 951–980 (2013)
- J.C. Hogg, P.D. Pare, T.L. Hackett, The contribution of small airway obstruction to the pathogenesis of chronic obstructive pulmonary disease. *Physiol. Rev.* **97**(2), 529–552 (2017)
- J.W. Duke et al. Premature birth affects the degree of airway dysanapsis and mechanical ventilatory constraints. *Exp. Physiol.* **103**(2), 261–275 (2018)
- A.H. Jobe, The new bronchopulmonary dysplasia. *Curr. Opin. Pediatr.* **23**(2), 167–172 (2011)