# Is The Excess Risk Of End Stage Renal Disease After Low Birth Weight Explained By Genetic Factors?

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## Background

A previous Norwegian study showed that low birth weight (LBW) conferred a 70% increased risk for end-stage renal disease (ESRD)[1]. Both LBW and ESRD do however cluster in families. To assess whether genetic factors could explain the association, we investigated risk of ESRD in subjects born with LBW, risk of ESRD in subjects with siblings born with LBW and the combined effect of own and sibling being born with LBW.

Reference

1. Bjørn Egil Vikse, Lorentz M. Irgens,Torbjørn Leivestad,_ Stein Hallan, and Bjarne M. Iversen: Low Birth Weight Increases Risk for End-Stage Renal Disease. *J Am Soc Nephrol* 19: 151–157, 2008.

## Material and methods

The Medical Birth Registry of Norway has registered data on all births in Norway since 1967. Sibling data have been registered in the Norwegian Population Registry for almost all births since 1953.
All patients with ESRD in Norway have since 1980 been registered in the Norwegian Renal Registry. We linked these registries and investigated whether risk of ESRD was associated with LBW in the index subject itself and/or LBW in at least one of its siblings. LBW was defined as birth weight less than the 10th gender-specific percentile (about 2.8 kg). Preterm birth was defined as gestational age less than 37 weeks and Small for gestational age (SGA) subjects was defined as birth weight less than the 10th percentile for gestational age using gender specific reference values in Norway.
Cox regression statistics were used for the analyses.

## Results

- Of the 1,865,217 included subjects born between 1967 and 2009, 532 developed ESRD. (Table 1)
- Compared with subjects without LBW and no siblings with LBW, subjects without LBW but a sibling with LBW had a relative risk (RR) of ESRD of 1.2 (95% confidence interval 0.9-1.6), subjects with LBW but no siblings with LBW had a RR of 1.6 (1.2-2.2) and subjects with LBW and a sibling with LBW had a RR of 1.8 (1.3-2.6) (Table 2).
- Corresponding RRs for SGA were 1.0(0.7-1.4),1.5(1.1-2.1) and 1.8 (1.2-2.5) (Table2).
- The relative risks remained virtually identical after adjustments for birth year, gender, maternal disease and maternal preeclampsia. Similar, but weaker, trends were observed when the analyses were done using preterm birth as exposure variable.
- LBW/SGA was also associated with increased risk of ESRD due to non-hereditary and non-congenital causes (For LBW, RR.1.4,p=0.05; For SGA,RR 1.6,p=0.001).

**Table 1; Characteristics of included subjects and their mothers' pregnancy health according to whether at least one sibling had low birth weight or were small for gestational age. Norway 1967-2009.**

| | Sibling with LBW | | Sibling with SGA | |
|---|---|---|---|---|
| | No | Yes | No | Yes |
| **N total** | 1,613,450 | 251,767 | 1,569,159 | 237,247 |
| **N ESRD** | 440 | 92 | 428 | 82 |
| **Mean number of siblings** | 1.7 ± 1.0 | 2.0 ± 1.0* | 1.7±1.0 | 1.9±1.1* |
| **Mean number years of follow-up** | 20.9±12.0 | 21.3±11.9* | 20.7±12.0 | 22.3±11.7* |
| **Proportion with birth weight percentile <10%** | 7.0 | 28.4* | 7.5 | 25.3* |
| **Proportion with SGA (<10th percentile)** | 7.4 | 25.0* | 7.0 | 27.7* |
| **Proportion with Preterm Birth** | 3.8 | 11.4* | 4.5 | 7.0* |
| **Proportion with maternal preeclampsia** | 2.4 | 4.1* | 2.5 | 3.4* |

* p-value < 0.001

**Table 2. Risk of end-stage renal disease in index subjects according to whether the index or at least one of its siblings had low birth weight. Norway 1980-2009.**

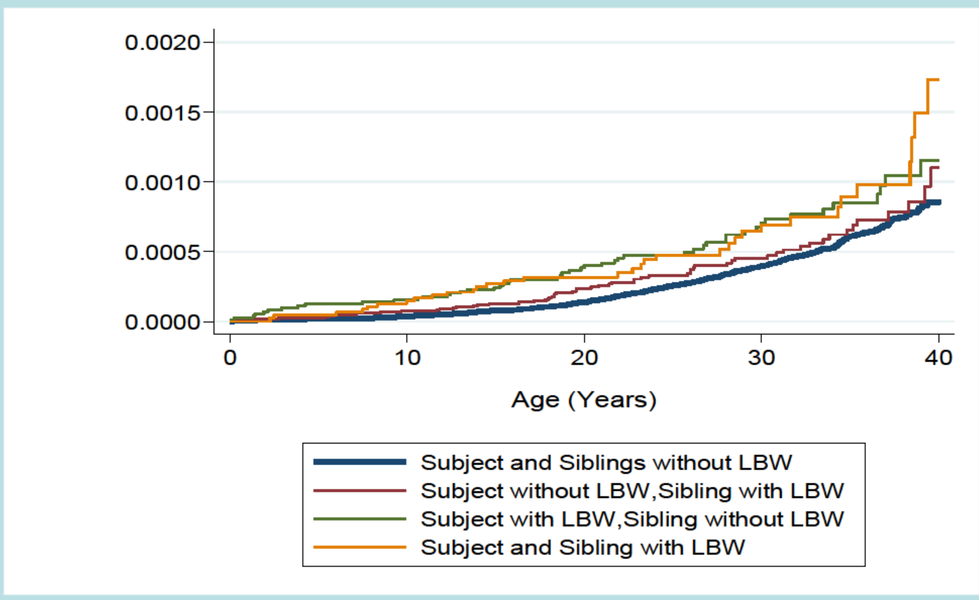
| Subject | Sibling | N-total | N-ESRD | Unadjusted Model | p-value | Adjusted Model* | p-value |
|---|---|---|---|---|---|---|---|
| **Not LBW** | Not LBW | 1,495,749 | 387 | 1.0 (ref) | | 1.0(ref) | |
| | LBW | 179,160 | 57 | 1.2 (0.9-1.6 ) | 0.2 | 1.2 (0.9-1.6) | 0.19 |
| **LBW** | Not LBW | 112,393 | 49 | 1.6 ( 1.2-2.2) | 0.02 | 1.6 (1.2-2.2) | 0.002 |
| | LBW | 70,944 | 34 | 1.8 (1.3-2.6 ) | 0.01 | 1.8 (1.3-2.5) | 0.001 |
| **Not SGA** | Not SGA | 1,381,988 | 351 | 1.0(ref) | | 1.0(ref) | |
| | SGA | 160,837 | 44 | 1.0(0.7-1.4) | 1.0 | 1.0 (0.7-1.4) | 1.0 |
| **SGA** | Not SGA | 103,855 | 47 | 1.5(1.1-2.1) | 0.007 | 1.5 (1.1-2.1) | 0.007 |
| | SGA | 61,668 | 33 | 1.8(1.2-2.5) | 0.002 | 1.8 (1.2-2.5) | 0.002 |
| **Not Preterm Birth** | Not Preterm Birth | 1,541,925 | 426 | 1.0(ref) | | 1.0(ref) | |
| | Preterm Birth | 101,770 | 33 | 1.2 (0.9-1.8) | 0.2 | 1.2 (0.9-1.8) | 0.3 |
| **Preterm Birth** | Not Preterm Birth | 63,546 | 21 | 1.3(0.9-2.1) | 0.2 | 1.3(0.8-2.0) | 0.3 |
| | Preterm Birth | 19,980 | 6 | 1.4 (0.6-3.2) | 0.4 | 1.3 (0.6-3.0) | 0.5 |

*Adjusted for Birth Year, Gender, Maternal Disease and Maternal Pre-eclampsia

**Table 3. RR for ESRD in different Age groups according to birth weight, Norway 1980-2009**

| Birth characteristic | Age 0 to 14yr | | | Age 15 to 24 yr | | | Age 25-42 yr | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | RR | p | N | RR | p | N | RR | p |
| **No LBW** | 98 | 1.00 | | 146 | 1.00 | | 200 | 1.00 | |
| **LBW** | 31 | 3.0 (2.0-4.6) | < 0.01 | 21 | 1.3 (0.8-2.0) | 0.3 | 31 | 1.3 (0.9-1.9) | 0.2 |
| **Siblings not LBW** | 101 | 1.00 | | 144 | 1.00 | | 195 | 1.00 | |
| **Sibling LBW** | 29 | 1.9 (1.2-2.8) | 0.004 | 26 | 1.1 (0.7-1.7) | 0.6 | 37 | 1.2 (0.9-1.7) | 0.3 |
| **No SGA** | 98 | 1.00 | | 132 | 1.00 | | 178 | 1.00 | |
| **SGA** | 22 | 2.1 (1.3-3.4) | 0.002 | 24 | 1.5 (0.9-2.5) | 0.09 | 40 | 1.6 (1.2-2.3) | 0.005 |
| **Sibling not SGA** | 101 | 1.00 | | 142 | 1.00 | | 185 | 1.00 | |
| **Sibling SGA** | 23 | 1.5 (0.9-2.3) | 0.1 | 24 | 1.0 (0.6-1.5) | 0.9 | 35 | 1.1 (0.8-1.6) | 0.5 |

**Fig 1; Risk of ESRD in subjects according to whether the subjects or at least one of its siblings had LBW.**




## Conclusion

LBW and SGA are associated with development of ESRD during the first 42 years of life

SGA is stronger than LBW in predicting increased risk for ESRD

LBW or SGA in siblings *did not confer excess risk* of developing ESRD. Thus, the excess risk associated with LBW/SGA does not seem to explained by genetic factors.

Our findings strengthens the hypothesis of intrauterine programming of nephron number as a risk factor for kidney disease.

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