

# **Under the skin**

**Early-life stress exposure and the co-occurrence of mental and physical health problems**

# Table of contents

<b>PREFACE</b>	<b>3</b>
Aknowledgements . . . . .	4
<b>INTRODUCTION</b>	<b>5</b>
References . . . . .	5
<b>I PART 1: The role of ELS in the development of mental and physical health</b>	<b>6</b>
<b>1 ELS and adolescent psycho-physical health</b>	<b>7</b>
Abstract . . . . .	7
1.1 Introduction . . . . .	8
1.2 Methods . . . . .	8
1.3 Results . . . . .	8
1.4 Discussion . . . . .	11
References . . . . .	11
<b>2 Lifestyle factors, ELS and adolescent psycho-physical health</b>	<b>12</b>
Abstract . . . . .	12
2.1 Introduction . . . . .	12
2.2 Methods . . . . .	12
2.3 Discussion . . . . .	12
References . . . . .	12
References . . . . .	12
<b>3 ELS and intracortical myelination</b>	<b>14</b>
Abstract . . . . .	14
3.1 Introduction . . . . .	14
3.2 Methods . . . . .	14
3.3 Discussion . . . . .	14
References . . . . .	14
References . . . . .	14
<b>4 ELS and cardiac morphology</b>	<b>16</b>
Abstract . . . . .	16
4.1 Introduction . . . . .	16

4.2	Methods . . . . .	16
4.3	Discussion . . . . .	16
	References . . . . .	16
<b>II</b>	<b>PART 2: Reciprocal relationships between mental and physical health problems</b>	<b>17</b>
	References . . . . .	18
<b>5</b>	<b>Longitudinal psycho-physical co-development</b>	<b>19</b>
	Abstract . . . . .	19
5.1	Introduction . . . . .	19
5.2	Methods . . . . .	19
5.3	Discussion . . . . .	19
	References . . . . .	19
	<b>DISCUSSION</b>	<b>20</b>
	References . . . . .	20
	References . . . . .	20
	<b>References</b>	<b>21</b>

# PREFACE

*“In the depth of winter, I found there was, within me, an invincible summer.”* Albert Camus  
– Summer (1954)

## AUTHOR

Serena Defina

## PROMOTOR

Henning Tiemier

## CO-PROMOTORS

Charlotte A.M. Cecil  
Janine F. Felix

### Note

This is a work in progress. Stay tuned :)

## Aknowledgements

TODO

# INTRODUCTION

Dear reader,

oh my good why does this not update

This an that (Fraser et al., 2013; R Core Team, 2021)

See Chapter [1](#) for additional discussion.

## References

## **Part I**

# **PART 1: The role of ELS in the development of mental and physical health**

# 1 ELS and adolescent psycho-physical health

Adapted from:

**Differential effects of pre- and postnatal early-life stress on internalizing, adiposity and their comorbidity**

**Defina, S.**, Woofenden, T., Baltramonaityte, V., Pariante, C. M., Lekadir, K., Jaddoe, V. W., Serdarevic, F., Tiemeier, H., Walton, E., Felix, J. F., & Cecil, C. A. M., \*on behalf of the EarlyCause Consortium. (2023). *JAACAP*. DOI

## Abstract

Objective: Depression and obesity are two highly prevalent and often comorbid conditions. Exposure to early-life stress (ELS) has been associated with both depression and obesity in adulthood, as well as their preclinical manifestations during development. However, it remains unclear whether: *(i)* associations differ depending on the timing of stress exposure (prenatal vs postnatal) and *(ii)* ELS is a shared risk factor underlying the comorbidity between the two conditions.

Method: Leveraging data from two large population-based birth cohorts (ALSPAC: n=8428 (52% male participants); Generation R: n=4268 (48% male participants)), we constructed comprehensive cumulative measures of prenatal (in utero) and postnatal (from birth to 10 years) ELS. At age 13.5 years we assessed: a) internalizing symptoms (using maternal reports); b) fat mass percentage (using dual-energy X-ray absorptiometry); c) their comorbidity, defined as the co-occurrence of high internalizing and high adiposity.

Results: Both prenatal (*total effect* [95%CI] = 0.20 [0.16; 0.22]) and postnatal stress ( $\beta$  [95%CI] = 0.22 [0.17; 0.25]) were associated with higher internalizing symptoms, with evidence of a more prominent role of postnatal stress. A weaker association (primarily driven by prenatal stress) was observed between stress and adiposity (prenatal: 0.07 [0.05; 0.09]; postnatal: 0.04 [0.01; 0.07]). Both pre- (OR [95%CI] = 1.70 [1.47; 1.97]) and postnatal stress (1.87 [1.61; 2.17]) were associated with an increased risk of developing comorbidity.

Conclusion: We found evidence of *(i)* timing and *(ii)* shared causal effects of ELS on psycho-cardiometabolic health in adolescence, but future research is warranted to clarify how these associations may unfold over time.



## 1.1 Introduction

In summary, this book has no content whatsoever (Elsenburg et al., 2017; Wiklund et al., 2008). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

## 1.2 Methods

## 1.3 Results

Table 1.1: My interesting caption.

<b>Sample descriptives</b>		
Generation R (GenR) and ALSPAC cohorts		
	<b>GenR</b> <b>(<i>n</i> = 4268)</b>	<b>ALSPAC</b> <b>(<i>n</i> = 8428)</b>
<b>Prenatal stress</b> , median (range)		
Total score	0.42 (0–2.60)	0.48 (0–2.34)
Life events	0.13 (0–0.67)	0.07 (0–0.57)
Contextual risk	0.25 (0–1.00)	0.25 (0–0.88)
Parental risk	0.00 (0–0.71)	0.10 (0–0.83)
Interpersonal risk	0.06 (0–0.95)	0.00 (0–0.84)
<b>Postnatal stress</b> , median (range)		
Total score	0.64 (0–3.59)	2.69 (0.17–16.43)
Life events	0.23 (0–0.82)	1.07 (0–3.50)
Contextual risk	0.20 (0–1.00)	0.50 (0–2.90)
Parental risk	0.00 (0–0.79)	0.57 (0–3.62)
Interpersonal risk	0.00 (0–0.79)	0.29 (0–5.49)
Direct victimization	0.13 (0–0.86)	0.00 (0–3.10)
<b>Internalizing score</b> , median (range)	4.00 (0–41)	1.00 (0–10)
<b>Fat mass percentage</b> , median (range)	24.7 (8.5–54.6)	23.9 (4.9–56.3)
<b>Outcome groups</b> , <i>n</i> (%)		
Healthy	2791 (65)	5916 (70)
High internalizing	623 (15)	795 (9)
High adiposity	631 (15)	1476 (18)
Comorbid	223 (5)	241 (3)
<b>Sex</b> , <i>n</i> (%)		
Male participants	2087 (48)	4370 (52)
Female participants	2181 (52)	4058 (48)
<b>Ethnic background</b> , <i>n</i> (%)		

Table 1.1: My interesting caption.

<b>Sample descriptives</b>		
Generation R (GenR) and ALSPAC cohorts		
Africa and Middle East <sup>a</sup>	115 (2.7)	
Asia and Oceania <sup>a</sup>	100 (2.3)	
Cape Verdean	100 (2.3)	
Dutch	2673 (62.6)	
Dutch Antillean	118 (2.8)	
Europe <sup>a</sup>	334 (7.8)	
Latin America <sup>a</sup>	72 (1.7)	
Moroccan	176 (4.1)	
North America <sup>a</sup>	25 (0.6)	
Surinamese	296 (6.9)	
Turkish	247 (5.8)	
<b>Age of the child</b> , median (range), years	13.5 (12.6–16.6)	13.5 (12.8–15.0)
<b>Pre-pregnancy BMI</b> , median (range), kg/m <sup>2</sup>	22.6 (14.4–50.2)	22.1 (12.5–48.6)
<b>Maternal smoking</b> , n (%)		
Never	3228 (76)	4412 (52)
Until (early) pregnancy	390 (9)	2524 (30)
During pregnancy	650 (15)	1492 (18)
<b>Maternal alcohol consumption</b> , GenR: n (%); ALSPAC: median (range)		
Never	1694 (40)	
Until early pregnancy	596 (14)	
Continued occasionally	1570 (37)	0.50 (0 – 3.5)
Continued frequently	407 (10)	
<b>Maternal education</b> , n (%) <sup>b</sup>		
Low	1716 (40.2)	4216 (50.0)
Medium	1278 (29.9)	3001 (35.6)
High	1274 (29.9)	1212 (14.4)
<b>Household income</b> , n (%) <sup>c</sup>		
Low	702 (16.4)	1318 (15.6)
Medium	2070 (48.5)	4324 (51.3)
High	1497 (35.1)	2786 (33.1)

Table 1.1: My interesting caption.

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**Sample descriptives**

Generation R (GenR) and ALSPAC cohorts

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Note: Sample descriptives pooled across 30 imputed datasets. BMI = Body-mass index.

<sup>a</sup> **Ethnic background grouping:**

Africa and Middle East = Iran (n=11); Iraq (10); South Africa (8); Angola (7); Eritrea (7); Israel (6); Cameroon (5); Egypt (5); Nigeria (5); Ethiopia (4); Algeria (3); Ghana (3); Lebanon (3); Liberia (3); Syria (3); Tanzania (3); Côte d'Ivoire (2); Guinea (2); Mozambique (2); Saudi Arabia (2); Senegal (2); Zimbabwe (2); Africa (1); Armenia (1); Burundi (1); Congo (1); French Congo (1); Gambia (1); Kenya (1); Mali (1); Mauritania (1); Palestine (1); Sierra Leone (1); Somalia (1); Sudan (1); Togo (1); Tunisia (1); Uganda (1); Yemen (1).

Asia and Oceania = Indonesia (n=23); Pakistan (9); Australia (6); China (6); Japan (6); Philippines (6); Thailand (6); India (5); Afghanistan (4); Hongkong (4); South Korea (4); Vietnam (4); Bangladesh (3); Korea (3); Taiwan (3); Kazakhstan (2); New Zealand (2); Dutch New Guinea (1); East Timor (1); Singapore (1); Sri Lanka (1).

Europe = Germany (n=55); Belgium (35); United Kingdom (30); France (29); Portugal (22); Spain (18); Yugoslavia (18); Poland (16); Italy (12); Bosnia-Herzegovina (11); Russia (10); Croatia (7); Czech Republic (7); Switzerland (7); Hungary (6); North Macedonia (6); Serbia-Montenegro (5); Denmark (4); Ireland (4); Norway (4); Sweden (4); Greece (3); Lithuania (3); Romania (3); Austria (2); Kosovo (2); Ukraine (2); Canary Islands (1); Estonia (1); Finland (1); Luxembourg (1); Madeira Islands (1); Moldova (1); Monaco (1); Slovakia (1); Slovenia (1).

Latin America = Colombia (n=18); Brazil (11); Dominican Republic (8); Chile (6); Venezuela (6); Cuba (4); Mexico (4); Argentina (3); Peru (3); Ecuador (2); Guyana (2); Belize (1); Bolivia (1); Haiti (1); Paraguay (1); Trinidad and Tobago (1).

North America = United States of America (n=16); Canada (9).

<sup>b</sup> **Maternal education:** low = “secondary, phase 2” or lower in GenR, “None”, “CSE”, “Vocational” or “O level” in ALSPAC; medium = “higher, phase 1” in GenR, “A level” in ALSPAC; high = “higher, phase 2” in GenR, “(College or university) degree” in ALSPAC. Categorization based on ISCED 2011.

<sup>c</sup> **Household income:** low = < €1600 /month in GenR, < £200 /week in ALSPAC; medium = between €1600 and € 4000 /month in GenR, between £200 and £400 /week in ALSPAC; high = > € 4000 /month in GenR, > £400 /week in ALSPAC.

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See Table 1.1 for descriptives.

## 1.4 Discussion

### References

- Elsenburg, L. K., Wijk, K. J. E. van, Liefbroer, A. C., & Smidt, N. (2017). Accumulation of adverse childhood events and overweight in children: A systematic review and meta-analysis [Journal Article]. *Obesity (Silver Spring)*, 25(5), 820–832. <https://doi.org/10.1002/oby.21797>
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## 2 Lifestyle factors, ELS and adolescent psycho-physical health

Adapted from:

The role of lifestyle factors in the association between early-life stress and adolescent psycho-physical health: Moderation analysis in two European birth cohorts

**Defina, S.**, Woofenden, T., Baltramonaityte, V., Tiemeier, H., Fairchild, G., Felix, J. F., Cecil, C.A.M., & Walton, E. (2024). *Preventive Medicine*. DOI

### Abstract

#### 2.1 Introduction

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

#### 2.2 Methods

#### 2.3 Discussion

### References

### References

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2012). Cohort profile: The 'children of the 90s'—the index offspring of the avon longitudinal study of parents and children [Journal Article]. *International Journal of Epidemiology*, 42(1), 111–127. <https://doi.org/10.1093/ije/dys064>

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., Henderson, J., Macleod, J., Molloy, L., Ness, A., Ring, S., Nelson, S. M., & Lawlor, D. A. (2013). Cohort profile: The avon longitudinal study of parents and children: ALSPAC mothers cohort [Journal Article]. *Int J Epidemiol*, 42(1), 97–110. <https://doi.org/10.1093/ije/dys066>

## 3 ELS and intracortical myelination

Adapted from:

Early-life stress exposure and intracortical myelination in childhood: a population-based neuroimaging study

**Defina, S.**, Manzoni, D., Tiemeier, H., Brouwer, R.M., Cecil, C.A.M., & Muetzel R.L. (*in preparation*)

### Abstract

#### 3.1 Introduction

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

#### 3.2 Methods

#### 3.3 Discussion

### References

### References

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2012). Cohort profile: The 'children of the 90s'—the index offspring of the avon longitudinal study of parents and children [Journal Article]. *International Journal of Epidemiology*, 42(1), 111–127. <https://doi.org/10.1093/ije/dys064>

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## 4 ELS and cardiac morphology

Adapted from:

Early-life stress exposure and heart morphology in childhood: a prospective population-based study

Defina, S., Kamphuis, A., Gaillard, R., & Felix, J. F. (*in preparation*)

### Abstact

#### 4.1 Introduction

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

#### 4.2 Methods

#### 4.3 Discussion

### References

## **Part II**

# **PART 2: Reciprocal relationships between mental and physical health problems**

## References

- Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2012). Cohort profile: The 'children of the 90s'—the index offspring of the avon longitudinal study of parents and children [Journal Article]. *International Journal of Epidemiology*, 42(1), 111–127. <https://doi.org/10.1093/ije/dys064>
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# 5 Longitudinal psycho-physical co-development

Adapted from:

Longitudinal co-development of depressive symptoms and cardio-metabolic risk factors from childhood to young adulthood

Defina, S., Cecil, C.A.M., Felix, J.F., Walton, E., & Tiemeier, H. (*under revision*)

## Abstact

### 5.1 Introduction

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

### 5.2 Methods

### 5.3 Discussion

## References

# DISCUSSION

See Chapter 1 for whatever whatever.

## References

## References

- Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., & Davey Smith, G. (2012). Cohort profile: The 'children of the 90s'—the index offspring of the avon longitudinal study of parents and children [Journal Article]. *International Journal of Epidemiology*, 42(1), 111–127. <https://doi.org/10.1093/ije/dys064>
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