

BMJ Paediatrics Open

BMJ Paediatrics Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Paediatrics Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjpaedsopen.bmj.com>).

If you have any questions on BMJ Paediatrics Open's open peer review process please email info.bmjpo@bmj.com

Confidential

	!
" # \$ \$!
% & ' \$	() # *% ' (\$+, " #)* -) *./ ### "/) / - \$! 0 !)1*" 2\$./ " \$ / 2 ! 3 2) " 4 2
5 6 #	%\$ #)%\$ #- \$!)%\$ #- \$)% %\$ #(\$

SCHOLARONE™
Manuscripts

Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

!! "# \$ % "' & ' "

(

) * + " " ! " , * - .) /

\$ 0 " 1 2* 3 "# " 4 !# % 5 " *

! % 4 % \$ 6 ! * 3 "# " * 7 77 !# %*

' (

, % \$ 5 % " ! * 5 " \$ 5 * 5 * (

/ % \$! 8 #* !# % 5 " * 9:; !# %* ' *

! % 4 % \$ 6 ! * 3 "# " (

< - # \$ ' ! < (

"

)

* 3 "# " 4 !# % 5 " * 9:; !# %* '

"() =! ""(" "

6 > ?@: 79 @; ,//

Confidential: For Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

' " 5 " ' "# \$ "" ! " >
 ">" "\$ % \$\$ > ! % "(
 " " ' " ! "> ;7,AB *' " "\$!
 " 5 "\$ % "' ! " >\$ \$ ' !% "
 %) (C "" "% D "1 "2 \$ "! >
 "" 5 % ! " ! " ! ! ' "" \$ ""
 ,99:A,9,(
 % ' * % \$" !! " "C
)" \$ > "" 5 % ! *,(97 1 (B7A,(B2* " ! !! \$
 "" *,(BE 1,(@,A(/E2* (" " > 5 "' \$ %
 "% ' \$ (; 1 (99A (@/2 \$ % " ! (/ 1 (9BA
 (B2 \$ \$ "" 5 % ! ()" ""\$
 "! % #" !% " "#" % % \$" ! (
 " % " " > \$ "\$ ' ">" " 5 \$
 ! * " % ! \$ % 5 ! " \$!
 \$" ! (
 "" F F\$" % ! (

/

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

"# \$ "" "%! ! " % ! (

<" ! % " \$! 5 \$! %

(

% " ! \$" ! * ! 5 > " ' 5

> ! % % !%" ' " (

" ' " \$ A % \$" ! '\$ " \$ ""

! " !% ' (

\$! " ""! ' "# \$ "" ' A

% \$" ! (

! % % !%" % ! > "# \$

"" \$ % \$" ! (

Confidential: For Review Only

@

5 " C !"* ! ! > " !* 5 > #
 %> \$ 5 !%*" ' 5 !" ' %! " ! 1 2
 " ' " % 1,2(" ! " "" > " >
 " \$! ! "> ' 5 " 1 \$ % \$ > " !*
 % ! C !" ! ! C " C!" ""2* " G A" H > !
 " 1/2 % " > !"
 5 "" % A ! 5 ! ! ! > '
 5 " " ! ! !%*" ! "" (- ' 0
 \$ % ! % ! \$ %) "" > ,9" 1@2(%
 A% 5 "*" "' " \$ > " ! ' ! " #
 5 > ! "" "" 5 " " 1E2(
 ' \$ " ! "*" !%% ! " 0 ! \$ % % ! " "
 !% ">" \$ % "(6 " ! ' "*" !
 % " ! * "> "" ! ' ! ! \$ %
 > %"* ! C * "" ! ! " " 1:2("% %*" "
 \$ % % ! " 5 ! "" "' ' ">" \$ % " "
 % ! " 0 !" \$ 5 " *(- \$ " ! C >
 % % > %" ! ! "" A " 172(
 ' " " " 5 " ' * !% %) ""
 "' " \$ A % \$ " ! * "' " \$ % " ! !
 * " "# \$ 5 " " ! ! " ! ! " " 1B* ;* 92(
 " > \$\$!" ! ! 5 % > % # ! 5 "
 > 1 2(

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

5 " \$ " ! ! " ! ! % > * " ' " "

\$! \$ % ! ! " * 5 ! > "" % >

% C " \$ % "# \$! " > \$! % 1 ((* ,2 (<

" * " ! \$! 5 " ! " 0 ! " ! \$ " ! 5

> 1/2(

! % " > % " > % "# \$! \$ 5

! % " \$ " ! " ' J * > % > 5 % " > ! " 1 @ *

E2(0 \$! " " % (5 " % " >

\$ " ! * ' \$ 0 ! " \$ \$ " \$ % " A \$ A % ! % "

> % \$ " ! 1 : * 72(" " > ! " " \$ " !

5 > 5 % > % "(< " ! " > " " "

' * " \$ " " (5 \$ A % ! % " " \$ % "

> \$ " ! ! * 5 \$ > # " ' \$ " "

1 B2(! ' % " C ! ! % " > " % %

> \$ \$ %) * > 5 ! 1/K2 " % " ! ! % A % \$ "

! 1 ;2(" " \$ % ! \$! % " > ' A > \$ \$ "

! * > "" ! " 1,92 ! ! \$ " ! C ! ! %

" > > " > % " * " " > " " \$!

% ! > 5 ' A > (

' * % " ! ' " ! % % % ;99L " * ! K \$

> ! " * \$! > \$ ' ! # > % "(;:9L " '

' \$! " 5 ! % ! " \$ " % " % >

> ! ! " % > \$! 5 > \$ (!

% ;79L " * % " ! " 5 > ' \$ " ! " > ! %

% \$ % \$ % " > " ! \$! ' ! > '

:

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

> "1,*,2(' ' " ;:9L" #
 ;79L"' > ! " ' ! (EA,(9K
 ! * % " ! ' 1B2(
 % \$ "" ' " C " \$ " !! " ' "
 !! " 5 " ' "# \$ "" \$\$ "> '
 \$\$ \$ %" \$ ">" ! \$! ! ! \$! * ' "#
 " \$\$ > ' \$ %" \$ "" * " \$ " " 1 (*
 "" 5 % ! 2* % " 5 \$ %"* " ! 1 (* " ! D
 " ! !! ' " " \$ "" 2(# !! ' ! %
 \$\$! " " ! \$ % ! > % # ! > ' A
 % \$ " ! ' 1 2*' " " \$ " \$! " \$! "# \$
 "" (
 " " ">" \$ % \$ % ' " " ""!
 ' 5 ' " 1,/*,@2(" " " ">" 0
 " %> "" > 1 % \$ % % 2 ' " " "(
 \$ % \$\$ " " ! > # " " %> "(" ">
 5 > ! " ! % % ! # % 1 (,9 @4@ EA/ 4E2(
 " " ! % " \$ 5 "> ;7,A ;B ' * !!
 " \$ 1 2*' 5 " ' ! %>
 / ,99E(" "" \$ ' \$ % + ,99: ! %> / ,9 , *
 ,EA@ " (- ! 4 5 " \$ " 5 "" \$
 6 AM " (\$ % > \$ > * \$ * " C
 \$ > ' " # " ">)" "(\$ "

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

!% A\$A % ! 1 2 % " >\$ B'" 5

\$ % 8 \$ " (

- " " \$ % ' ! " " \$! ' 1 N: B2'

> >\$ \$ ' " 1 N: B2'

' "A> ' " ' "A> 5 "((

1 NB*B7B2 \$ \$! \$> > " \$' " * 5 "

' "A> 5 > > 6 AM " * 5

' >\$ " ! > F ">)" 1 N E2

! \$ % \$ " 9 " 1% \$ E(, "2

! >\$ B(!% " > 1 N;/9*:@@2

' "A> 5 "' " ' "A> > 5 "

6 AM " * ' ! \$!% >\$ \$

B(

' ! " \$ "" ' ! \$ \$ 'A ,99:A,9 , 1 2 \$ "

! \$ " " "" 5 % ! 1 A! 9: 2 ' " > \$ %

' " " ! > " * 1,2 \$ " " ! D ! "

"! ' "" \$ "" 5 " 1</,A</; A 92

"! " (

* * " "> !% * %! ! " \$ > % #

! ' 5 \$ % ,99E >" \$

" ! > 6 # "("' 5 0 "

! " " ! " \$!% ! > C "*" \$ 5 >

! " % " " !! \$ % 5 > " ! " ' (

B

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

"" ! " \$ > ! \$ " ! ,99B
 G! H \$ % " \$ ' L" " ! "*" !# %*
 M > 6 % * G ' H!5 % > !%% "*"
 G H!5 % (" \$ " 5
 !% \$ % % % 4" \$ % % 5 %> ,99E 5 ! 5
 "! > \$ " " ! 5 " (;1\$ \$
 !% " " ! * EA : "2' 5 \$ % ! "
 ' ! " % ") > ' " ! " ! " ' (
 "" % ;B7A ;: \$ ' M "" " >
 ! "" \$ " ! \$ % 1 2 E 1 C! 2(

 C D "% "' " "% D " 1 2
 ! " ;EK \$ " " \$ "" 5 % ! " " ! " !
 ' "" \$ "" " \$ > 5 (" % \$\$ 'A ' " !!%
 \$ % + ,99: \$ \$ " " " 4 \$\$ " % "" 45 " * \$
 \$ % " \$ " \$\$ 'A !%> ,9 /(
 (% \$! % " \$ % " !% C*
 " !)! " 5 5 % \$! " !" \$
 ! 5 % > " % " \$ % (5 "" 1 2
 ' 5 " ' ! ! 5% !% \$ % "
 \$ " ! ' " ! " > ' \$% '
 "% " ! " J ""* " " ! ! 5% !%
 % !% ")! "\$ % \$" ! ("" * ' \$
 ! " 6 *)" \$ * \$> > 4 " ! "
 % "" \$ \$\$!" \$! ! (" \$\$! \$! * \$

;

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

)" % \$! " 0 ! " \$ \$! * ' " ! 6 ,) " \$
5 " EA: 6 / \$) " \$ % % 4 ! %
(" " " ! ! " 5 " , @ (9 ()
> " " ! ! " ! " \$ " " (" ' %
\$ \$ % " ! % " ' " " (% " ! " '
" ' ! 1;9K \$ " \$ \$ 2 * ' "
% \$ > > ' \$ " ! > 1@:K2(" C ! \$ %
!! " ! > > 5 * % " ! " ' % \$ "
"> ;7,A7@ \$ " ! % \$;7EAB (% " !
" " ! % % % " \$ " "(< " !
" " ! % # " ; * " ! ! 5 % ' "
! % (% " ! " % 5 " !
! 5 % > ' ! % " \$ " ! ()
AAAAAAA > > AAAAAAAA
" > , % " * !! % ! ! \$ "" 5 % ! ' "
,K % ,K ' % (" ! ! " ' \$
% \$ % \$ " ! * ' ,7K \$ % /;K \$ ' % (< "
"! !! ' "" \$ "" * !! % ! ! ' " /K %
:K ' % (< % \$ " ! " ! ! "
" \$ " ! % F /K \$ ' % ,K \$ % ()
AAAAAAA > , > AAAAAAAA
C "" % " \$ \$\$! " \$ \$! "" ! % "
" > / (% " * " 6 * ') " \$ \$ > *
4 > " ! (% ' * 5 "

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

" ! " D " 1 "2 \$ > !% "*" ,(97 1;EK
(B7A,(B2 \$ "" 5 % ! * ,(BE 1,(@,A(/E2 \$ " " ! !!
' "" \$ "" (% " ! " "% "#" \$
"" 5 % ! * " (/ 1 (9BA (B2 (; 1 (99A (@/2 " ! 5 * '
\$ " ! !! \$ "" "' "*" (@E 1 (/@A (E72
!% 9(;/ 19(:/A (/B2 % " ! "(! "" ! !
" \$! \$\$!"\$ \$ " ' !% "(
)" "\$ \$! ")! \$ %! *!"
% #" 6 , !% % % 6 /* " "#" %
\$ " ! * " " "% \$ C! "" "#" \$ "" \$ % \$ "
! "' "" ! ' " % \$! "("*" '5 * %
% 5 \$ \$ % \$ " ! \$ "
(
AAAAAAAA > / > AAAAAA
" ! " \$ " " > 5 \$ " "% " "
*!% ' \$ " ! * \$! " " "" ! ' !
"# \$ "" 5 % ! " ! !! ' "" \$ ""
(! * % % !% * " "" > ! " 0 ! " \$ \$! *
" "#" % \$ " !
5 " " ! ' " " " ">" \$% " 5 " ' \$ "
! ! "" 5 ! "% \$ " ! !! " ! ! "*
"# \$ " ! " 1,E* ,:* ,72(% " "
" " "" ! ! \$ "" 5 " "% > % \$!

> C!"" "# \$" ! 5 " \$ \$ % \$" ! !% '

" ' 1,E2(

\$" ! " " > "! % #" !%

5 "*" ! \$ " ' ! %!0 \$! " > !%

"" \$! ' \$ \$" ! (5 " ' " " " 5 " ' *

" "% ! 5 !% ! 1;2* " \$ %> "! * !

! 5 " 5 > % # ! " " \$" ! *

' " ! ' 1 2("*" \$%

5 % \$\$!" ! 5 ! " >\$ " !

"*" ! "0 !" > % # ! \$ "G" H !

! 5% \$ \$ % \$" ! % > %! "% ! C

\$ "" 1,B2(

"# " % "\$ \$" ! "

! \$ % "5 !% \$ " "! !! *!% '

"" 5 % ! (" " ' 5 " " "*" ' "" ""!

' ! 5 " "> # "# \$! " "

"" 5 " "*" " ""> \$ "\$ % % 1E2(

" " \$ "" " "" ! % "# \$ ""

""! ' ! 5 " (!# 5 *' "D

% %! "% " 5 "> " > % !>

! % >" |> \$! ">" "1,;2(< % 5 %

" ! 5 *"\$ *"! *"> ! A\$A % !% " #

0 " "\$!5 \$ % " 5 " " ' > \$ # \$!

1/92(% ! \$" > " > " "" ' ! "

%> \$!% C !" !" \$% \$\$! "

1
2
3 1/ *,2(' A# ' \$\$! "\$ " \$ % 5
4 " " % ! ">" > %"' !!"" % " 5!" 1//2(
5
6 \$ "! > 5 # > ! " "' ' ! !
7
8 > ' 5 " A" %*' ' " 5 " \$! " 5
9
10 > # "" % % " 1/@2(*M %*- ! <"
11
12 1/E2 5 % " 0 ! 5 % " % D
13
14 " > D \$! " 5 " ! ()
15
16
17
18
19
20 % " \$ "" " " \$ ' " " " "\$
21
22 %\$ 'A ' % % 0 (% % " !# \$
23
24 \$ % > \$% "#\$! "*" *\$! C " "
25
26 " "(" \$ 0 ' ' ' "! ' \$ " * '5 *
27
28 ' %"! " ' ! ' \$" ! " \$!!!\$!% "
29
30 % ! ! > C! % \$! \$"!!!\$ ()
31
32
33
34
35
36 "" " "" ! !! \$ % "% 5 \$
37
38 "# \$ "" ""! ' ! 5 " (< " "' \$"
39
40 ! ! ! 5 \$\$! \$!% " > ()
41
42
43
44
45
46
47 " "" *! " \$ ""* "
48
49 ' \$ " \$ \$ " ! (+ - . ! \$ " *
50
51 " " 5" \$(" 5 5 \$ 5 " \$
52
53
54 % "! ()
55
56
57
58
59
60

/

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

"" '"" > \$ % - # \$ ' ! < 9A9E @ (

" 5 !% "" (

(< M* % " * * ' #* + (\$\$! \$! 5 "

! (! " ! 6 *,99:F :9 ,/A ,/B(

,(* % + * ! (" \$ \$\$!" \$! !

% % ! O" > 5 % > %"(> "

,99@,B ,:EA ,7B(

/(A- #)" * 3 6* 3 %" (A A 5 %

%)! " \$ \$ 5 \$ 'A \$

" % "" (! ,9 7F/B; E;/A E@B(

@(M > * 8 % "" - ' 3 (- ! " 0 ! " \$!

% % A ! % ! "(! ,99:F/7/ :BIB (

E(. * * ("" (% % ! " \$ 5 > ! " \$

"" % ! % "" % A "(% + " !

,9 ,F ;; @ AE (

:(6 D * M ' * > * (% \$ # \$

> ! " * \$\$!* 3*,99/(

7(- " M* "" 6* < M (1,9 :2(5 ! \$ % " "

% ! " ! " ! ' \$ "" % "" % ! 5 ' % A

"(6 ! 1- % 2 ,9 :F;E ,:,,(

B() * > < (.) -(! * " ! ! ""* " !

%)" % ! " ' ! " (! ,99,F/:9 @@/A@@B(

;(.) -* < DP *) * > < (% ! % \$\$" !

"" "\$ % ' " ! " "(< D* * - * "(' "\$"

! ' #& 5 ! \$! % "" + "" ! 3 " * 3*,99* ,9:A,,9(

9(. - !D "# ""# *) * > < * .) -(! > 5

" ' " ! " (! " ! " !

% ,99:F@ ;EA 9,(

(.) -*) (5 * ! " \$A" ! % " \$ A

% \$ " ! 5" (5 5 ,9 F// ,@B;A,@;@(

@

1
2
3 ,(3*8 % (5 " C ! " % ! !
4 \$ % \$ " ! 5 ! \$ % " 5 " (> "
5 ,97F:@ 7A,;(

6
7 /(.)D 6* ! "+* A- # + (" !
8 5 % " !(6!! -*.)D 6* +\$\$ <((* "(
9 ' % " " !* !! !(6 ! "
10 5,9 F7:*BA/9(
11
12 @ (6* A- # +* - !# (5 A" ! \$! " ! !
13 " \$\$! " \$ " 5 (6 ! " 5,9 F7:* "" (

14
15 E (6* *6! 3* % " (" D
16 > ! ! " 0 ! " ! % \$ "(" ! 5,9 9F,9 @ @A@,;(

17
18 :(! "+* !# * ' +* - > " A ! 6 (> # '
19 !! * " ! % ! "(" ! 8 # !* ""(
20
21 7(" % 6* ! * 8 % (" \$ " ! 5 '
22 % A "" (5 5,997F,; E/A7:(

23
24 B (.) -* Q" 6(! % > # ' " % \$ " ! A
25 ' " " (< % ! 8 # ,9 7F,, EA,E(
26
27 ;(% * > <*.) -*) (! " A \$ A %
28 ! ! " (! ,997F,; @/7A@@,(

29
30 ,9(> 6* O * R* ! (% ! \$! % " >
31 > 5 ' A > \$! \$ " ! (! " ,997F ; //:A/@@(
32
33 ,(- % * 6(! \$ % "" "" ' * ;79(
34
35 ,(S\$ -(5 "# !# % ; BA ;7/ T' " "
36 !# % ; BA ;7/U !# % " (* ' * ,99 (
37
38 ,/(5 "" +\$* "" * #> % ((C 5 ' 5 \$
39 ' " " (-6 > ! ,9 F * @E9(
40
41 ,@(8 % # -* %% * < 6 (' ' " " ! >
42 " AA "\$ % ! % ! " ! C ! \$ % \$ "
43 " C % "(% ! % \$,997F : 7,;A7/E(
44
45 ,E () *.) -* > <(5 > % % ! ' \$
46 ! " ! " ! " (+ % %%
47 ,99@FEB @ ,A@ 7(
48
49 ,:(.) -*) ("% \$ " ! ! " % ' ' '
50 " ! ! ! A ' " ! " (+ " !
51 ,9 @F:B : A : ;(
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

,7(.) -*) * > <(! % " "5 " ! !
% > % \$ % ! ' \$! "AA ! " (+ " !
"! ,99:F@77,/A7//(
,B(-)S# " % * % * .) * - (" "\$! *
"! \$ % ! " ! !! D " " " \$; / ; ;
5 " !# % (+ % %% ,9:F79 @7/A@B9(
;:(- % 6* 5 "" (!% " "" "\$ % " "(
- D "# * !! 6 "(" ! \$ (C\$ 5 " ""*
* ; ; 9(
/9(-(\$ " > \$ \$ " ! 5 % " ! 5 (
< ,99@F @ /9A@7(
/(8 > " * - * -(!% " > \$! A \$ A % ! (
8 \$ * ,999F7 ; : @A : / , (
/,(+ % " * "5 # + * % (+ * " 3(! " \$ %
" 5 ! " AA \$ \$ " ! !% ! (6 5 " ,99@F : ,7A @ (
//(# " + * ' " 6 * M 6(5 ! % !% "\$
! A \$ A % ! " (" ! " ,9 9F
B 9(
/@(3 \$ % + * (\$\$! " \$ " "" > " ! \$!
% ! "\$ " " > ' ! % % "" (
5 " ! ,99 F / @E A @7 (
/E((% \$\$ -* . 88(> \$ "" " %
' " ! 5 (+ " ! ,99EF :: 7*EA /(
/:(3 * M % 3 " * - ! + * < " (" > \$! \$ " !
% % ! " % > 5 (5 " ! >
,9 @FE: @9:A E(

:

> (

					!	"
			N: B	NB*77B	N * E	;/9*:@@
C	6	E:(/B(E	@:(@	E (@	
	8 %	@/(;	:(E	E9:(@B:(
	4					A
\$ " !	9 A , % "	;9(/	@,(E	@E(E		
	/A,@ % "	;(7	E7(E	E@(E		A
\$ >	;7,A7@	E9(/	,/(/9(,	/,(:	
	;7EA77	,7(7	/,(B	,:(9	,:(@	
	;7BAB	,,(9	@@/(@/(B	/B(9	
6 #" ; M	6 5	,(;;	/(9B	,(EE	/,	
! ,99E	V ; "	9(9	9(,	/E(,	;/	
	9A , "	EE(,	E9:(E@;(@:(
	/? "	/@(B	/;,(;;	@ (E	
! % 0 " ,99E	< "	(B	@:(,:(/,	
	!	7(/	7(B	,@,(B(/	
		;(@	,9(E	,/(,9(,	
	<	,/(:	,@(@	:(,	,,(7	
	< \$,7(B	,,(:	9(E	,E(:	
% 5 %> ,99E		7;(9	::(7	E/(/	7/(@	
,99E		/(/	,@(B	,(/	,9(
M ! " !		@,(;	E,(B	/7(7	@,(;	
	'	@/(;	/;(@@(:	@/(;	
		/(/	B(B(E	/(/	

> ,(

#

\$

6 8 % 6 8 %

" M ,/(, (: /(@ E(B

% " ! " ,(,;(/(, E(,

" @ ,@(! EE B

< " ! ,:(B /;((B /(E

\$ > ;7,A7@ ,(, ,(E /(E(/

;7EA77 ,(@ , (7 /(@ E(7

;7BAB ,(@ , (9 /(7 :(/

" ! ,99E V ; " ;(9 ,(@ 7(: , (E

9 / , " ,(, /(/(€ :,(

/ ? " ;(: (B ,(@ (/

4 % ,99E , @ (7 /E(, ;(/ ,(7

! % 0 " ,99E < " 7(,(E E(; B(7

! E(,E(@ (7(,

/(; ,(/ @ (E(;

< (7 B(E /(@ (:

< \$ B(B @ (7 (; /(E

M ! " ! ,(, ,(/(@ E(B

' ,(€ ,(, /(€ E(;

,(/ ,(@ /(€ E(;

,(/ , (7 /(@ E(B

B

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

> /(
%

		&		
	6		6 ,	6 /
	1;EK 2		1;EK 2	1;EK 2
M				
% " !	" (; 1 (99A (@/2	(, 19(;A (/@2	(/ 19(;@A (/E2	
	" (/ 1 (9BA (B2	(9: 1 (9 A (2	(9E 1 (99A (92	
< " !	, (97 1 (B7A, (B2	(: @ 1 (@7A (B/2	(@@ 1 (;A (: 2	
		\$		
M				
% " !	" 9(/ 19(:/A (/B2	9(BE 19(E7A (,72	9(B: 19(EBA (,;2	
	" (@E 1 (/@A (E72	(/, 1 (,A (@@2	(/9 1 (;A (@ 2	
< % \$ " !	, (BE 1, (@,A(/E2	, (9 1 (:BA, (@ 2	(:, 1 (/EA (;@2	

6 ")" \$ * \$ > > 4 " !(
6 , " ")" \$ % 5 " (
6 / " ")" \$!% 0 " % % 4> "
(

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

* - ;

Confidential: For Review Only

BMJ Paediatrics Open

Can adoption at an early age protect children at risk from depression in adulthood? A Swedish National Cohort Study.

Journal:	BMJ Paediatrics Open
Manuscript ID	bmjpo-2018-000353.R1
Article Type:	Original article
Date Submitted by the Author:	02-Nov-2018
Complete List of Authors:	Hjern, Anders; Centre for Health Equity Studies, ; Palacios, Jesus; Universidad de Sevilla, Development Psychology Vinnerljung, Bo; Stockholms Universitet Samhällsvetenskapliga Fakulteten, Social Work
Keywords:	Child Abuse, Child Psychology, Child Psychiatry, Comm Child Health

SCHOLARONE™
Manuscripts

Can adoption at an early age protect children at risk from depression in adulthood? A Swedish
National Cohort Study.

Anders Hjerrn¹, Jesus Palaciós², Bo Vinnerljung³

¹ Centre for Health Equity Studies (CHESS), Karolinska Institutet/Stockholm University, and
Clinical Epidemiology/Department of Medicine, Karolinska Institutet, S 171 77 Stockholm,
Sweden.

² Department of Developmental Psychology, University of Seville, Seville, Spain.

³ Department of Social Work, Stockholm University, S 106 91 Stockholm, Sweden, and
Clinical Epidemiology/Department of Medicine, Karolinska Institutet.

Funding: Bank of Sweden Tercentenary Foundation.

Corresponding author:

Anders Hjerrn

CHESS, Karolinska Institutet/Stockholm University, S 106 91 Stockholm, Sweden

anders.hjerrn@chess.su.se

Mobile phone: +46 70 491 12 33

Abstract

Objective

Our aim was to investigate whether the risk of depression in adulthood in children raised by substitute parents from an early age differ by care arrangements.

Methods

Register study in Swedish national cohorts born 1972-81, with three study groups of children raised in adoptive or foster homes with care starting before the age of two and a comparison majority population group. Cox regression estimated hazard ratios (HRs) of prescribed antidepressive medication and specialised psychiatric care with a diagnosis of depression in adulthood during 2006-2012.

Results

Compared with the general population, long term foster care carried the highest age and sex adjusted HR for both antidepressive medication, 2.07 (1.87-2.28), and psychiatric care for depression, 2.85 (2.42-3.35), in adulthood. Adults raised by adoptive parents were far more similar to the general population with HR of 1.19 (1.00-1.43) for domestic and 1.13 (1.08-1.18) for international adoption for antidepressive medication. Adjusting the analysis for school marks and income attenuated these risks more in the long term foster care group.

Conclusion

The study demonstrates the benefits of early adoption when substitute parents are provided for young children, and underlines the importance of improved educational support for children in foster care.

Key words: depression; adoption; foster home care.

1
2
3
4
5 What is already known on this subject
6

7 The risk of depression in adulthood is much increased in maltreated children.
8

9
10 Foster care and adoption are the main types of care provided for children maltreated at
11 an early age.
12

13
14 Compared to those placed in foster care, adopted children have been shown to have
15 better educational and employment outcomes in the adult Swedish population.
16
17
18

19
20
21 What this study hopes to add
22

23 Adults with a history of long-term foster care had twofold rates of depression
24 indicators compared with the general population.
25
26

27
28 Adoption during infancy is associated with a risk of adult depression lower than long-
29 term foster care.
30
31

32
33 Poorer educational and employment outcomes may contribute to the higher risk of
34 depression in former foster children.
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

Early adverse experiences, particularly child abuse and neglect, have been linked to a number of negative outcomes, with longitudinal evidence showing the impact on physical (1) as well as on mental health (2). Research on stress neurobiology is helping to gain a better understanding of the connections between early adversity (in the form of abuse and neglect, traumatic experiences and chronic exposure to toxic stress), its “deep-seated” neurobiological alterations (3) and later mental health disturbances.

Literature reviews and meta-analytic evidence highlight the connection between early adversity and poor psychiatric outcomes, including depression. Between a quarter and a third of maltreated children meet criteria for major depression by their late 20s (4). Compared to non-maltreated individuals, those with a history of abuse and neglect are twice as likely to develop both recurrent and persistent depressive episodes (5).

In welfare societies, one common consequence of maltreatment in early childhood is placement into substitute families. Maintaining these children with their parents, or placing them in residential care, has been associated with a higher incidence of mental health problems, including anxiety, depression and conduct disorders (6). At the same time, studies from many countries have consistently shown that growing up in substitute families does not eliminate the ill consequences of early adversity. Both adopted and fostered children exhibit more mental health problems –including depression– than those in the general population (7). Swedish population studies have shown that, compared to majority population peers, young adults with a history of long-term foster care, as well as of domestic and intercountry adoption, present higher risk for various psychological and psychiatric disorders (8, 9, 10). Considerable differences in educational achievement and labor market participation have also been reported (11).

1
2
3 The higher levels of psychological and psychiatric morbidity in adulthood, as well as
4 of poor educational performance indicators, have typically been assumed to be related
5 primarily to exposure to familial risk factors before placement (e.g., 12). For the international
6 adoptees, specific adverse consequences related to early neglectful institutional care have
7 been reported (13).
8
9

10
11
12
13
14 Age at placement has been demonstrated to be an important risk factor for negative
15 outcomes later in life such as lower IQ, problem behavior and emotional disturbances (14,
16 15). Type and quality of care also seem to play a role. Adoption provides more stability than
17 foster care, with frequent changes of foster families and other out-of-home care arrangements
18 being inherent to long term foster care (16,17). This instability causes fostered children to
19 develop behavioral and mental health problems. Foster care instability is also present in
20 Sweden, the setting of this study. Even for long-term placements that last from early years
21 until the beginning of adolescence, every fourth breaks down during the first teenage years
22 (18). Adopted children in Sweden may also experience placement instability at some time
23 before age of majority, but the prevalence (3%) is miniscule compared to long-term foster
24 care (19). In their analysis of the impact of placement stability on the well-being of foster
25 children, Rubin and associates (20) concluded that foster children experience placement
26 instability unrelated to their baseline problems, and that this instability has per se a significant
27 impact on their behavior and well-being.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

47 In Sweden, domestic adoption was common in the mid 1900's, including around 1% of
48 birth cohorts, often children born out of wedlock by young mothers. During the 1960's new
49 welfare policies that provided economic support for single mothers and a more liberal
50 abortion policy gradually decreased the number of children available for adoption. Since the
51 mid 1970's, domestic adoptions have been rare in Sweden and foster care has become the
52 main form of long term substitute care for young children who cannot be reunited with their
53
54
55
56
57
58
59
60

1
2
3 birth parents (21,22). International adoption in Sweden was initiated in the 1960's and peaked
4
5 in the 1970's when birth cohorts in Sweden included 1.5-2.0% internationally adopted
6
7 children, at that time the highest per capita proportion in the world (8).
8
9

10 The aim of this study was to exploit this period of drastic changes in Swedish
11 adoption practices to investigate whether the risk of depression in adulthood differs between
12 different forms of substitute care for children placed in care in infancy, and whether risk
13 patterns differ between the lighter forms of depression, treated outside of hospitals (i.e.,
14 antidepressive medication), and more severe forms, treated in hospital care (i.e., specialized
15 psychiatric care with a diagnosis of depression). Taking into account the well documented
16 differences in school performance and labor market participation between adopted and long-
17 term foster children in Sweden (11), we also wanted to explore if these factors influence their
18 risk of depression.
19
20
21
22
23
24
25
26
27
28
29

30 Methods

31
32
33 This study is based on information from Swedish national registers, containing data
34 with high validity and low attrition rates (23, 24). These registers are based on the unique
35 personal identity number assigned at birth (or time of immigration) to all Swedish residents.
36
37 Data from different registers can be linked using these identity numbers. Our study has been
38 approved by the ethics committee in the Stockholm region (No. 2014/415-31/5).
39
40
41
42
43
44

45 The study population is comprised of individuals born 1972-1981 who, according to
46 the Register of the Total Population (RTP), were alive and resident in Sweden on December
47 31 2005. This population was followed up from January 1 2006 to December 31 2012, at age
48 25-41 years. Biological and/or adoptive parents of these individuals were identified in the
49 Multi-Generation Register. Information about region of birth, year of adoption, sex and year
50 of birth in RTP was linked to the study subjects and their parents. Data on age at first
51
52
53
54
55
56
57
58
59
60

1
2
3 placement in out-of-home care (OHC) and time spent in OHC before age 18 was retrieved
4
5 from the National Child Welfare Register.
6

7
8 Based on this information we created three study groups of children who had entered
9
10 OHC or been adopted before the age of two years: Domestic adoptees (N=618) were
11
12 Swedish-born and had two registered Swedish-born adoptive parents.. International adoptees
13
14 (N=8,878) fulfilled the criteria of being born outside of western Europe, having at least one
15
16 Swedish-born adoptive parent but no birth parent in the Multi-Generation register, and having
17
18 entered Sweden before their second birthday; Long term foster care subjects (N=1 115) had
19
20 no record of adoption and a total time in OHC of at least 10 years (median of 15.2 years) in
21
22 care before age 18. A comparison population labelled Majority population (N=930,944), all
23
24 Swedish-born individuals with at least one Swedish-born birth parent and no adoptive parents
25
26 in the Multi-Generation register, and with no record of placement in OHC before the age of
27
28 18.
29
30

31 32 33 Depression

34
35 Two indicators of depression were created for the follow-up 2006-2012: (1) first
36
37 indication of dispensed antidepressive medication (AC-code N06A) was obtained from the
38
39 Swedish Prescribed Drug Register, (2) first entry in outpatient specialized care or a hospital
40
41 discharge with a diagnosis of depressive disorder (F32-F39 in ICD-10) into the National
42
43 Patient Discharge Register.
44
45

46 47 Socio-demographic and educational covariates

48
49 Data on age, gender, disposable income, domicile and indicators of labor market
50
51 participation were retrieved from the 2005 Longitudinal Integration Database for Health
52
53 Insurance and Labor Market Studies. Disposable income was divided into quintiles, and
54
55 included all registered sources of income deducted by taxes, and thereafter divided by
56
57 consumer units in the household according to a formula developed by Statistics Sweden.
58
59
60

1
2
3 Domicile was split into three categories and defined by the place of residence in 2008: “city”
4 referred to the metropolitan areas of Sweden’s three largest cities, Stockholm, Gothenburg
5 and Malmo, “town” covered other predominately urban communities, and “rural” covered the
6 remainder. Labor market participation was defined as having an income from employment
7 /self employment in November 2005 or having received societal benefits as an active student
8 that year. School marks in grade 9 (final year of compulsory school, 15-16 years) were
9 retrieved from the National School Register which is administered jointly by the Swedish
10 School Authority and Statistics Sweden. The grading system during 1987-1996 nationally
11 followed a Gaussian distribution and consisted of a scale from 1 (Poor) to 5 (Excellent).
12
13
14
15
16
17
18
19
20
21
22

23 Statistical analyses

24
25
26 Cox proportional hazards models were used to estimate hazard ratios (HR) and
27 corresponding 95% CI for dispense of antidepressive medication and hospital specialised care
28 with a diagnosis of depression as defined above. Person time of follow-up was accumulated
29 from January 2006 until the date of the first dispense/date of first admission/visit, date of
30 death from the National Cause of Death Register or end of follow-up in December 2013.
31
32
33
34
35
36

37
38 The modelling of early childhood determinants of adult mental health is complex, since
39 trajectories potentially involve intermediate factors that are products of the early childhood
40 environment but also determinants of adult mental health. In a previous study (11) we have
41 shown that the educational achievement and income of young adult men raised in foster care
42 in Sweden is considerably lower than that of men in the general population with the same test
43 scores on IQ tests, suggesting that educational achievement and income are important
44 components in trajectories from foster care to adulthood. In this study, we therefore
45 considered Model 1, adjusted only for gender, and urban/rural residency as category variables
46 and year of birth as a continuous variable, as the main analysis of the effects of care in early
47 childhood. To study the effect of care, after adjustment for potential consequences of type of
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 care , we also created a Model 2 adjusted for grade point averages at age 15-16 and a Model 3
4
5 further adjusted for employment/income in adult age. All analyses were conducted using
6
7 SPSS version 24.0.
8

9 10 Results

11
12 Table 1 shows the characteristics of the study groups. International adoptees were more
13
14 often females in comparison with the other study groups. The domestic adoptees were the
15
16 youngest when entering care (90% during their first year of life), with international adoptees
17
18 more often being adopted between their first and second birthday (46%). As expected from
19
20 the policy change describe above, the domestic adoptees were more often than the other study
21
22 groups born in 1972-74 and the foster children more often during 1975-81. The domestic
23
24 adoptees had the highest income and employment rates of the study groups. Foster children
25
26 had the lowest school marks in grade 9, the lowest educational achievement and the lowest
27
28 income. Domestic and international adoptees had mean grade point averages and educational
29
30 achievement in between the comparison population and the foster children.
31
32
33
34

35 ----- Table 1 in about here -----
36

37
38 As Table 2 demonstrates, the accumulated incidence of antidepressive medication was
39
40 12% in men and 21% in women in the general population. The highest incidences were found
41
42 among the former foster children, with 27% for men and 39% for women. For hospital
43
44 psychiatric care with a diagnosis of depression, the accumulated incidence was 3% in men
45
46 and 6% in women in the general population. Former foster children had the highest incidences
47
48 also for this outcome; 13% for women and 12% for men.
49
50

51 -----Table 2 in about here-----
52

53
54 Cox regression models of the effects of type of care on depression outcomes are
55
56 presented in Table 3. In the main analysis, presented in Model 1, we adjusted for year of birth,
57
58 gender and rural/urban residency only. Compared with the general population, individuals in
59
60

1
2
3 the foster care group had the highest hazard ratios (HRs) for both outcomes, 2.07 (95% CI:
4 1.87-2.28) for antidepressive medication, and 2.85 (2.42-3.35) for hospital psychiatric care
5
6 with a diagnosis of depression. International and domestic adoptees had similar risks for
7
8 antidepressive medication, HRs 1.13 (1.08-1.18) and 1.19 (1.00-1.43) respectively, while the
9
10 HR for psychiatric care for depression was higher in international adoptees, 1.45 (1.34-1.57)
11
12 compared to 0.93 (0.63-1.38) in the domestic adoptees. Interaction analyses could not detect
13
14 any significant gender differences for any of these two outcomes.
15
16
17
18

19 Adjusting the analysis for factors on the trajectory from childhood to adulthood, school
20
21 marks in Model 2 and income and employment in Model 3, attenuated these risks more in the
22
23 foster care group, suggesting that some of the excess risks for depression in the former foster
24
25 children was indeed associated with these intermediate factors. HRs, however, remained
26
27 more elevated for former foster children than for the adoption groups and the general
28
29 population.
30
31
32

33 -----Table 3 in about here-----
34

35 Discussion

36
37 This national cohort study of adults raised by adoptive or foster parents demonstrates
38
39 that, compared with foster care, adoption during the infancy years is associated with a lower
40
41 risk of antidepressive medication and psychiatric care with a diagnosis of depression in
42
43 adulthood. Education, employment and income, as possible consequences of type of care,
44
45 attenuated these risks more in the foster care group
46
47
48

49 Previous research on Swedish adults raised in substitute families have shown that foster
50
51 children consistently have a higher consumption of psychiatric care and psychotropic drugs,
52
53 and a higher risk of suicidality than adoptees (25, 26, 27). The pattern demonstrated in this
54
55 study suggests that a higher incidence of depressive disorders may be an important factor
56
57
58
59
60

1
2
3 behind the excess risk of suicide previously found in former foster children compared with
4
5 international adoptees in Sweden (25).
6

7
8 In the foster care group the HRs were strongly attenuated by school marks and income
9
10 levels, although the percentage of those with higher academic qualifications and better income
11
12 is significantly lower for the foster care group. Previous Swedish studies have shown that,
13
14 despite a similar cognitive competence (9), adoptees perform better in school, reach higher
15
16 educational levels and have higher labor market participation than adults raised in foster care,
17
18 with the international adoptees doing particularly well (11). Thus, family related
19
20 environmental differences in cognitive and educational support before and during the school
21
22 years, and the consequences on labor market participation of this “stunted” educational
23
24 achievement for the former foster children may be one mechanism that can explain their
25
26 higher rate of depression (28).
27
28
29

30
31 The risk estimates for the foster children and the international adoptees were
32
33 particularly high for the more severe outcome of hospital psychiatric care, compared with
34
35 antidepressive medication. This is in line with previous studies, where depression associated
36
37 with childhood adversity has been linked to a greater risk of recurrent and persistent
38
39 depressive episodes, and also to less benefits from treatment (5).
40
41

42
43 The results of this study suggests that early adoption can limit the risk of depression
44
45 associated with early childhood adversity. Lacking detailed individual data, we hypothesize
46
47 that an important mechanism is that adoption provides better stability and a more predictable
48
49 childhood home base – both for children and substitute parents (29). From a developmental
50
51 perspective, safety, security, stability and nurturance in out-of-home placements are key
52
53 requisites for the recovery from past adversities and the wellbeing of looked after children
54
55 (30). The importance of stability is highlighted by studies showing that an increase in the
56
57 number of OHC placement experiences predicts a greater rate of mental health difficulties
58
59
60

1
2
3 (31,32). The well-known difficulties for youth transitioning from OHC to independent living
4
5 also seem to include substantial problems with access to adult mental health services (33).
6
7

8 Our findings can be putatively linked to neurobiological studies showing the connection
9
10 between early adversity and the HPA-system, with persistent high levels of cortisol having
11
12 been linked to adult depression in animal models (34). Laurent, Gilliam, Bruce and Fisher
13
14 (35) have demonstrated that a high quality caring environment has the potential to normalize
15
16 and stabilize the daily pattern of cortisol levels in early childhood.
17
18

19 20 Strengths and Limitations

21 The main strength of this study is the use of the Swedish national registers that allows for long
22
23 term follow-up with minimal attrition and high quality data. The main limitation is the lack of
24
25 information about familial risk factors, ie hereditary, foetal and early childhood exposures in
26
27 the study groups and the reason for why the children were taken into foster care or were
28
29 adopted. In a previous study, where we had access to more information about the birth
30
31 parents, we showed that the birth parents of national adoptees as well as children in long term
32
33 foster care have much higher cumulated incidences of psychiatric disorders and substance
34
35 abuse than the general population, with the long term foster children having the highest
36
37 incidences. Thus, it seems probable that foetal exposures to substances and genetic risk
38
39 factors for depression explain some of the differences between the study groups (11). The use
40
41 of a unique window in Swedish child welfare history, however, when domestic adoptions
42
43 were replaced with foster care as the default choice for placements in maltreated young
44
45 children can be expected to limit the influence of such confounding.
46
47
48
49
50

51 Another type of potential confounding would have to have been considered if adopted
52
53 children and/or foster children were offered targeted psychiatric services that would increase
54
55 the chance of receiving psychiatric care and having been being prescribed antidepressive
56
57 medication in adulthood. Such targeted services, however, are not in place in Sweden today
58
59
60

1
2
3 and were not in place when the studied populations were children. This and other studies
4
5 indicate that such services should be considered (37).
6
7

8 Conclusions

9
10
11 This study suggests that early adoption can protect children from some or even all of the
12 risk of depression associated with early childhood adversity. Further studies within the foster
13 care group are needed to elucidate the protective effect of placement stability.
14
15
16
17
18
19
20

21 Contributions

22
23 AH designed this study, created the dataset for analysis, planned and analysed the data and
24 wrote first draft of this article. JP and BV participated in the planning of the study, interpreted
25 the results and revised the draft. All authors have read and approved the final version of the
26 manuscript.
27
28
29
30
31

32 Funding

33
34 This study was supported by a grant from the Bank of Sweden Tercentenary Foundation P10-0514:1.
35

36 Competing interests

37
38 The authors have no competing interests to report.
39
40
41
42
43

44 References

- 45
46
47
48
49
50
51 1. Flaherty EG, Thompson, R, Litrownik, AJ et al. Effect of early childhood adversity on
52 child health. Arch Pediatr Adolesc Med,2006;160:1232-1238.
53
54
55
56
57
58
59
60

- 1
2
3 2. Ethier LS, Lemelin Jp, Lacharite C. A longitudinal study of the effects of chronic
4 maltreatment on children's behavioral and emotional problems. *Child Abuse*
5
6
7
8 *Negl*,2004,28:1265-1278.
9
- 10
11 3. Sonuga-Barke Ejs, Kennedy M, Kumsta R et al. Child-to-adult neurodevelopmental
12 and mental health trajectories after early life deprivation: the young adult follow-up of the
13 longitudinal English and Romanian Adoptees study. *Lancet* 2017;389:1539-1548.
14
15
16
17
- 18
19 4. Gilbert R, Widom Cs, Browne K et al. Burden and consequences of child
20 maltreatment in high-income countries. *Lancet* 2009;373:68–81.
21
22
23
- 24
25 5. Nanni V, Uher, R. Danese, A. Childhood maltreatment predicts unfavorable course of
26 illness and treatment outcome in depression: a meta-analysis. *Am Jn Psychiatry*
27
28
29 2012;169:141-51.
30
- 31
32 6. Meltzer H, Gatward R, Corbin, T et al. The mental health of young people looked after
33 by local authorities in England, The Stationery Office, UK, 2003.
34
35
36
- 37
38 7. Bronsard G, Alessandrini M, Fond G et al. (2016). The prevalence of mental disorders
39 among children and adolescents in the child welfare system: a systematic review and meta-
40
41
42
43
44 analysis. *Medicine (Baltimore)* 2016;95:e2622.
- 45
46 8. Hjern A, Lindblad F. Vinnerljung B. Suicide, psychiatric illness, and social
47 maladjustment in intercountry adoptees in Sweden: a cohort study. *Lancet* 2002;360: 443-448.
48
49
- 50
51 9. Vinnerljung B, Franzén E, Hjern A, Lindblad F. Long term outcome of foster care:
52 Lessons from Swedish national cohort studies. In Fernandez, E, Barth R, eds. *How does foster*
53
54
55
56
57
58
59
60 care work? International evidence of outcomes, Jessica Kingsley, UK, 2010, 206-220.

- 1
2
3 10. Von Borczyskowski A, Hjern A, Lindblad F, Vinnerljung B. Suicidal behaviour in
4 national and international adult adoptees: a Swedish cohort study. *Soc Psychiatry Psychiatr*
5
6 *Epidemiol* 2006;41:95-102.
7
- 8
9
10 11. Vinnerljung B, Hjern A. Cognitive, educational and self-support outcomes of long-
11 term foster care vs adoption. *Child Youth Serv Rev* 2011;33:2489-2494.
12
- 13 12. Turney K, Wildeman C. Adverse experiences among children placed in and adopted
14 from foster care: Evidence from a nationally representative study. *Child Abuse Negl*
15
16 2017;64:117-129.
17
- 18 13. Van Ijzendoorn MH, Palacios J, Sonuga-Barke EJS et al. Children in institutional care:
19 Delayed development and resilience. In Mccall RB, Van Ijzendoorn MH, Juffer F. et al., eds.
20 *Children without permanent parents: Research, Practice and Policy. Monogr Soc Res Child*
21 *Dev* 2011;76,8-30.
22
- 23 14. Rutter M, Sonuga-Barke EJS, Beckett C et al. Deprivation-specific psychological
24 patterns: effects of institutional deprivation. *Monogr Soc Res Child Dev* 2011;76,issue 1.
25
- 26 15. Sheridan MA, Drury S, Mclaughlin KA, Almas A. Early institutionalization:
27 Neurobiological consequences and genetic modifiers. *Neuropsychol Rev* 2010;20:414-429.
28
- 29 16. Palacios J, Rolock N, Selwyn J, Barbosa-Ducharne MA. Adoption breakdown:
30 concept, research and implications. *Res Social Work Prac*,in press.
31
- 32 17. Oosterman M, Schuengel C, Wim Slot N et al. Disruption in foster care: A review and
33 meta-analysis. *Child Youth Serv Rev* 2007;29:53-76.
34
- 35 18. Vinnerljung B, Sallnäs M. Placement breakdowns in long term foster care - a regional
36 Swedish study. *Child Fam Soc Work* 2017;22:15-25.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 19. Elmund A, Lindblad F, Vinnerljung B, Hjern A. Intercountry adoptees in out-of-home
4 care: a national cohort study. *Acta Paediat* 2007;96:437-442.
5
6
7
- 8 20. Rubin DM, O'Reilly ALR, Luan X, Localio AR. The impact of placement stability on
9 behavioral well-being for children in foster care. *Pediatrics* 2007;119:336-344.
10
11
12
- 13 21. Bohman, M. Adopted children and their families, Proprius, Sweden, 1970.
14
15
16
- 17 22. Nordlöf B. Svenska adoptioner i Stockholm 1918-1973 [Swedish adoptions in
18 Stockholm 1918-1973] Stockholms Stad., Sweden, 2001.
19
20
21
- 22 23. Ludvigsson Jf, Andersson E, Ekbohm A. et al. External review and validation of the
23 Swedish national inpatient register. *BMC Public Health* 2011;11, 450.
24
25
26
- 27 24. Wettermark B, Hammar N, Forede CM et al. The new Swedish Prescribed Drug
28 Register--opportunities for pharmacoepidemiological research and experience from the first
29 six months. *Pharmacoepidemiol Drug Saf* 2007;16:726-735.
30
31
32
- 33 25. Hjern A, Vinnerljung B, Lindblad F. Avoidable mortality among child welfare
34 recipients and intercountry adoptees: a national cohort study. *J Epidemiol Community Health*
35 2004;58:412-417.
36
37
38
- 39 26. Vinnerljung B, Hjern A. Consumption of psychotropic drugs among adults who were
40 in societal care during their childhood--A Swedish national cohort study. *Nord J Psychiatry*
41 2014;68:611-619.
42
43
44
- 45 27. Vinnerljung B, Hjern A, Lindblad F. Suicide attempts and severe psychiatric
46 morbidity among former child welfare clients--a national cohort study. *J Child Psychol*
47 *Psychiatr* 2006;47:723-733.
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 28. Björkenstam E, Dalman C, Vinnerljung, B et al. Childhood household dysfunction,
4 school performance and psychiatric care utilization in young adults: a register study of 96 399
5 individuals in Stockholm County. *J Epidemiol Community Health* 2016;70:473-480.
6
7
8
9
10
11 29. Bohman M, Sigvardsson S. Outcomes in adoption: lessons from longitudinal studies.
12 In Brodzinsky D, Schechter M eds. *The psychology of adoption*. Oxford University Press,
13 USA, 1990.
14
15
16
17
18 30. Harden BJ. Safety and stability for foster children: a developmental perspective.
19 *Future Child* 2004;14:30-47.
20
21
22
23
24 31. Webster D, Barth R, Needell B. Placement stability for children in out-of-home care.
25 *Child Welfare*, 2000;79:614-632.
26
27
28
29 32. James S, Landsverk J, Slymen D.J., Leslie LK. Predictors of outpatient mental health
30 service use--the role of foster care placement change. *Ment Health Serv Res* 2004; 6:127-141.
31
32
33
34
35 33. Akister J, Owens M, Goodyer IM. Leaving care and mental health: outcomes for
36 children in out-of-home care during the transition to adulthood. *Health Res Policy Syst* 2010;
37 8:10.
38
39
40
41
42 34. Kaufman J, Charney D. Effects of early stress on brain structure and function:
43 implications for understanding the relationship between child maltreatment and depression.
44 *Dev Psychopathol* 2001;13:451-471.
45
46
47
48
49
50 35.. Nemeroff CB, Vale WW. The neurobiology of depression: inroads to treatment and
51 new drug discovery. *J Clin Psychiatry* 2005;66:Suppl 7,5-13.
52
53
54
55
56
57
58
59
60

1
2
3 36. Laurent HK, Gilliam Ks, Bruce J, Fisher PA. HPA stability for children in foster care:
4 mental health implications and moderation by early intervention. Dev Psychobiol
5
6 2014;56:1406-15.
7
8
9

10
11 37. Vinnerljung, B. Hjern, A. Guest editorial. Health and health care services for children in
12 out-of-home care. Int J Soc Welfare 2018;27:321-324.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1.
Characteristics of the study population.

		Domestic adoptees N=618	International adoptees N=8,778	Foster care N=1,115	General population 930,944
Sex	Men	56.1	38.5	49.4	51.4
	Women	43.9	61.5	50.6	48.6
Age at adoption/entry into foster care	0 -12 mths	90.3	42.5	45.5	-
	13-24 mths	9.7	57.5	54.5	-
Year of birth	1972-74	50.3	23.1	30.2	32.6
	1975-77	27.7	32.8	26.0	29.4
	1978-81	22.0	44.1	43.8	38.0
Marks in 9 th Grade	Mean average	2.99	3.08	2.55	3.21
Education in 2005	V 9 year	10.0	10.2	35.2	9.3
	10-12 years	55.2	50.6	54.9	49.1
	13+ years	34.8	39.2	9.9	41.5
Income in quintiles in 2005	First	11.8	14.6	26.1	13.2
	Second	17.3	17.8	24.2	18.3
	Third	19.4	20.5	23.1	20.2
	Fourth	23.6	24.4	16.2	22.7
	Fifth	27.8	22.6	10.5	25.6
Employed November 2005		79.0	69.7	53.3	73.4
Student in 2005		13.0	24.8	12.3	20.1
Geographic residency	City	42.9	52.8	37.7	42.9
	Town	43.9	39.1	44.6	43.9
	Rural	13.3	8.1	8.5	13.3

Table 2.

Depression indicators by socio-demographic variables. Percentages.

		Medication		Hospital care	
		Men	Women	Men	Women
Study groups	General population	12.3	21.6	3.4	5.8
	Domestic adoptee	12.1	29.2	3.2	5.2
	International adoptee	14.1	24.0	5.5	8.1
	Foster care	26.8	39.1	11.8	13.5
Year of birth	1972-74	12.2	22.5	3.1	5.3
	1975-77	12.4	21.7	3.4	5.7
	1978-81	12.4	21.0	3.7	6.3
Highest education in 2005	< 9 years	19.0	29.4	7.6	12.8
	10-12 years	12.2	23.1	3.4	6.2
	13+ years	9.1	16.8	2.1	4.3
Student and/or employed in 2005	No	24.7	35.2	9.3	12.7
Income in quintiles in 2005	First	17.1	22.5	5.9	8.7
	Second	15.1	25.1	4.5	7.2
	Third	13.9	22.3	4.0	5.9
	Fourth	11.7	18.5	3.1	4.6
	Fifth	8.8	14.7	1.9	3.5
Geographic residency	City	12.2	21.1	3.4	5.8
	Town	12.4	22.2	3.4	5.9
	Rural	12.3	22.4	3.4	5.7
Total		12.3	21.7	3.4	5.8

Table 3.

Cox regression models of indicators of depression and different forms of substitute care.

	Antidepressive medication		
	Model 1	Model 2	Model 3
	HR (95% CI)	HR (95% CI)	HR (95% CI)
General population	1	1	1
Domestic adoptees	1.19 (1.00-1.43)	1.12 (0.93-1.34)	1.13 (0.94-1.35)
International adoptees	1.13 (1.08-1.18)	1.06 (1.01-1.11)	1.05 (1.00-1.10)
Foster children	2.07 (1.87-2.28)	1.64 (1.47-1.83)	1.44 (1.29-1.61)
	Hospital care		
General population	1	1	1
Domestic adoptees	0.93 (0.63-1.38)	0.85 (0.57-1.27)	0.86 (0.58-1.29)
International adoptees	1.45 (1.34-1.57)	1.32 (1.22-1.44)	1.30 (1.19-1.41)
Former foster children	2.85 (2.42-3.35)	2.01 (1.68-2.41)	1.62 (1.35-1.94)

Model 1 is adjusted for gender, year of birth and urban/rural residency.

Model 2 is also adjusted for mean grade point averages in ninth grade.

Model 3 is also adjusted for income in quintiles and employment/being a student in young adulthood.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Confidential: For Review Only