# Strategies to improve the outcome of biliary atresia

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# Course of life into adulthood of patients with biliary atresia: the achievement of developmental milestones in a nation-wide cohort

Submitted

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Chapter 7

**ABSTRACT**

**Background**

**C**hildren who are growing up with a chronic disease often have delayed developmental milestones. Little is known regarding the achievement of developmental milestones ("course of life") into adulthood of patients with biliary atresia (BA), with or without orthotopic liver transplantation (OLT)

**Aim of the study**

**T**o determine the course of life of young adults who had been diagnosed with BA in infancy.

**Methods**

All patients from the Dutch nationwide BA registry, aged between 18 and 30 years, were invited to complete a validated Course of Life Questionnaire. This questionnaire is designed to assess the course of life of young adults who grew up with a chronic or life-threatening disease. It consists of developmental milestones (autonomy, psychosexual and social development) and risk behavior (antisocial behavior, substance use and gambling). Data from transplanted and non-transplanted adult BA patients were compared with existing data from an age-matched Dutch reference group (n=508).

**Main results**

Forty BA patients (23 males) completed the questionnaire (response rate 74%). Mean age was 23.4±3.5 years. Twenty-five were not transplanted, while fifteen underwent OLT. No significant differences were found in the achievement of developmental milestones and antisocial behavior between the three groups. Substance use and gambling, especially lesser use of alcohol, were significantly less prevalent in the transplanted patients compared to the reference group (p=0.01), but not compared to the non-transplanted patients.

**Conclusions**

As opposed to most patients growing up with chronic diseases, BA survivors are not delayed in the achievement of developmental milestones compared with the reference group. Transplanted BA patients report less risk behavior.

## INTRODUCTION

Biliary atresia (BA) is a cholestatic disease of infancy, which is universally fatal if left untreated. Due to obliteration of the bile ducts a profound cholestasis develops in the first weeks of life. It is a rare disease, with a prevalence varying from 1/15.000 to 1/19.000 live births in Western Europe and the USA.[22,67,111,210] The last few decades it has changed from being fatal to a disease for which treatment is available. The current treatment is a Kasai portoenterostomy, in which the extra-hepatic fibrotic bile ducts are resected and a portoenterostomy is constructed, aiming to restore bile flow.[82] However, even if the Kasai procedure has been successful, liver fibrosis often progresses due to damage of the intrahepatic bile ducts. Ultimately, the vast majority of BA patients will have to undergo liver transplantation due to the development of liver cirrhosis.[60,103] Patients with BA are at risk for complications such as cholangitis, or for cirrhosis associated complications as oesophageal varices bleeding, which may require frequent hospitalization.[103] Furthermore, chronic liver disease may be associated with fatigue and pruritus.[76,87]

BA may have a substantial impact on course of life (COL). COL, described as fulfilling developmental tasks and achieving developmental milestones, is important in the adjustment to adult life.[49,96] Development of autonomy, a developmental milestone, is positively related to both ego development and general health outcomes.[40] Thus, retardation in development may have significant consequences for later functioning.

With the novel treatment options for children with BA becoming available, more and more children will reach adulthood and physicians will therefore encounter an increasing number of young adult patients surviving BA. From recent studies it is known that the COL of adolescents who grew up with a chronic disease is often delayed. In general, children with a chronic disease have reached fewer milestones, or fulfilled these milestones at an older age, when compared to the general population.[166] Yet, significant differences have been observed between diseases.[166] Patients with severe and life-threatening diseases, such as childhood cancer and end-stage renal disease, achieved fewer milestones in all domains. In contrast, COL of patients with esophageal atresia is comparable to that of the reference group. Risk behavior, in terms of 'trying out', can be seen as part of the development from teenager to becoming an adult. It is possible that young adults who grew up with a chronic disease are more aware of the vulnerability of their health and thus show less risk behavior.[199] Therefore, risk behavior is relevant from a developmental psychological point of view.[165]

As yet, no information is available regarding COL in children or adults surviving BA with or without native liver. Information on COL is valuable to gain insight in the extent to which BA patients reach several developmental milestones and to determine if and which interventions are needed to minimize developmental delay in BA patients. The aim of this study was to examine the COL in young adults with BA. We hypothesized that COL is delayed in adults with BA with or without orthotopic liver transplantation (OLT) when compared to an age-matched reference group from the general population. It is important to distinguish non-transplanted and transplanted BA patients, as these patients suffer from a different course of their disease. We expected that survivors of BA have reached less developmental milestones and tasks than their peers and show less risk behavior.

## METHODS

*Patients*

All Dutch BA patients who underwent a Kasai portoenterostomy for BA between 1977 and 1991, and who where over 18 years of age at the time of the study were eligible (n=54). Data of these patients

were retrieved from the NeSBAR (Netherlands Study group on Biliary Atresia Registry) database and the Groningen pediatric OLT database. In each patient, the diagnosis of BA was confirmed in infancy by intra-operative cholangiography and pathology of the resection specimen. Patients were treated in one of the six centers specialized in pediatric surgery and in the single Dutch pediatric OLT center located in Groningen. Patients suffering from psychiatric disorders were excluded (one patient). Clinical patient data included most recent laboratory measurements (aspartate aminotransferase (ASAT), bilirubin, and albumin), gender, age at OLT, current age and comorbidities. The study was performed according to the guidelines of the local medical ethical committee.

*Questionnaires*

All eligible patients received a letter of invitation explaining the goal of the study by mail. This letter included the Course of Life Questionnaire (COLQ), an informed consent form and a prepaid envelope. The COLQ has been developed to investigate the COL of young adults who have grown up with a chronic or life-threatening disease.[54] It consists of five subscales: 1) autonomy development (6 items), 2) psychosexual development (4 items), 3) social development (12 items), 4) antisocial behavior (4 items), and 5) substance use and gambling (12 items). Higher scores on the first three scales indicate the accomplishment of more developmental milestones, while higher scores on the last two scales imply an increase in risk behavior. Questions in the COLQ retrospectively ask whether the respondent achieved certain milestones or at what age these milestones were reached. The psychometric qualities of this instrument have been reported to be good to satisfactory.[165]

The reference group consisted of a random cohort of 508 patients between 18 and 30 years of age, who were randomly retrieved from general practitioners in the Netherlands. The results of this group were described previously.[165] They filled in the COLQ in 2000 and 2001.

*Statistical analysis*

Demographics and clinical characteristics of responders and non-responders were compared to detect possible confounders, using the Chi-square test or Fisher's exact test for categorical data and the Student's T-test or Mann-Whitney U test for continuous data. ANOVA was used to examine possible differences in mean scores between the two BA patient groups and the reference group. For categorical variables with large samples (≥ 5) the Chi-square test was used. The Fisher exact test was used for categorical variables with smaller samples. For all analyses the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois) version 16.0 was used.

## RESULTS

*Patients*

Of the 54 eligible patients, 40 patients returned the questionnaire (response rate 74%): 25 patients had not received transplantation and 15 patients underwent OLT. One BA patient in the non-transplanted group also had cystic fibrosis. Excluding the patient with cystic fibrosis had no effect on the outcome of all results.

Table 1 compares demographics and clinical characteristics of responders and non-responders. Non-responders in the transplanted group had a significantly lower serum albumin compared to responders (p=0.02). None of the responders were below the reference value for serum albumin of 35 g/L. Of the transplanted non-responders, one patient was below the reference value, with a serum albumin of 30 g/L. There were no differences between the study groups and the reference

group in age (p=0.19) and gender (p=0.20).

**Table 1:** Demographics and clinical characteristics of responding and non-responding BA patients and comparison between the two study groups.

| | BA non-transplanted | | | BA OLT | | | Reference Group |
|---|---|---|---|---|---|---|---|
| | Responders | Non-responders | P-value | Responders | Non-responders | P-value | |
| **Number** | 25 | 5 | | 15 | 9 | 0.08* | 508 |
| **Gender (% female)** | 48% | 60% | 1.0 | 33% | 78% | 0.09 | 53% |
| **Age at survey (years)** | 23 (19-30) | 24 (20-32) | 0.49 | 22 (19-31) | 22 (19-32) | 0.82 | 24 (18-31)[§] |
| **Age at Kasai (days)** | 58 (35-117) | 64 (48-68) | 0.83 | 60 (43-126) | 46 (32-175) | 0.17 | NA |
| **Age OLT (years)** | NA | NA | - | 5 (1-17) | 12 (1-15) | 0.61 | NA |
| **Second OLT** | NA | NA | - | none | none | - | NA |
| **Current bilirubin (µmol/L)** | 17 (5-71) | 14 (6-46) | 0.72 | 17 (5-36) | 16 (5-23) | 0.31 | NA |
| **Current ASAT (U/L)** | 27 (6-160) | 77 (20-101) | 0.06 | 30 (16-96) | 40 (23-77) | 0.17 | NA |
| **Current albumin (g/L)** | 41 (36-54) | 40 (39-40) | 0.19 | 47 (42-49) | 43 (30-47) | 0.02 | NA |
| **Additional congenital malformations** | none | none | - | none | none | - | NA |

Data expressed as median (range). *χ2-test of the distribution of responders and non-responders over the two study groups. NA: not applicable. [§]expressed as mean (range).

*COL subscales*

Table 2 shows the scores on the five subscales of the COLQ. ANOVA showed one significant difference between the three groups, namely in substance use and gambling. Consequent analysis showed that transplanted BA patients reported significantly less substance use and gambling than the reference group (p=0.01).

**Table 2:** Subscales of the COLQ in adult non-transplanted and transplanted BA patients and in the reference group

| Scales mean (SD) | BA non-transplanted n=25 | BA OLT n=15 | Reference group n = 449 | F | p-value |
|---|---|---|---|---|---|
| **Autonomy development** | 9.5 ± 1.7 | 8.7 ± 1.8 | 9.4 ± 1.5 | 1.26 | 0.20 |
| **Psycho-sexual development** | 7.2 ± 1.3 | 6.5 ± 1.4 | 7.2 ± 1.1 | 2.84 | 0.06 |
| **Social development** | 21.7 ± 2.2 | 19.9 ± 3.2 | 21.0 ± 2.5 | 2.41 | 0.09 |
| **Antisocial development** | 5.0 ± 1.1 | 4.4 ± 0.6 | 4.7 ± 1.0 | 1.81 | 0.17 |
| **Substance use and gambling** | 14.2 ± 3.0 | 13.4 ± 2.0 | 15.1 ± 2.6 | 4.34 | 0.01* |

*Significant difference between BA OLT and the reference group (p=0.01).

*Developmental milestones, item level*

Comparison of the scores of the developmental milestones on item level showed three differences (Table 3). Transplanted patients were older at the time they had their first girlfriend/boyfriend (p=0.01) and fewer were member of a sports club at primary school (p=0.01) than young adults in the reference group. There was a significant difference between the three groups in going out to a bar or disco at secondary school, but not between two separate groups.

**Table 3:** Developmental milestones in adult non-transplanted and transplanted BA patients and in a reference group, and comparison of the study groups. Data depict absolute number (percentage).

| | BA non-transplanted (n=25) | BA OLT (n=15) | Reference group (n=508) | P-value |
|---|---|---|---|---|
| **Autonomy development** | | | | |
| *Regular job in your family, primary school* | | | | |
| Yes | 12 (52) | 4 (27) | 233 (46) | 0.27 |
| No | 11 (48) | 11 (73) | 273 (54) | |
| *Paid jobs, primary school* | | | | |
| Yes | 11 (46) | 7 (47) | 170 (34) | 0.33 |
| No | 13 (54) | 8 (53) | 326 (66) | |
| *Regular job in your family, secondary school* | | | | |
| Yes | 16 (64) | 7 (47) | 304 (60) | 0.53 |
| No | 9 (36) | 8 (53) | 201 (40) | |
| *Paid jobs, secondary school* | | | | |
| 18 or younger | 18 (78) | 11 (73) | 443 (87) | 0.14 |
| 19 or older/never | 5 (22) | 4 (27) | 64 (13) | |
| *On holiday without adults* | | | | |
| 17 or younger | 13 (52) | 5 (33) | 268 (53) | 0.33 |
| 18 or older/never | 12 (48) | 10 (67) | 239 (47) | |
| *Leaving your parents place* | | | | |
| Not living with parents | 14 (56) | 7 (47) | 328 (65) | 0.26 |
| Still living with parents | 11 (44) | 8 (53) | 180 (35) | |
| **Psychosexual development** | | | | |
| *First girlfriend/boyfriend* | | | | |
| 17 or younger | 18 (72) | 8 (53) | 407 (80) | 0.03* |
| 18 or older/never | 7 (28) | 7 (47) | 99 (20) | |
| *Falling in love for the first time* | | | | |
| 18 or younger | 23 (92) | 14 (93) | 462 (92) | 0.97 |
| 19 or older/never | 2 (8) | 1 (7) | 42 (8) | |

**Table 3,** continued

| | | | | |
|---|---|---|---|---|
| *Sexual intimacy for the first time* | | | | |
| 18 or younger | 21 (84) | 10 (67) | 421 (83) | 0.24 |
| 19 or older/never | 4 (16) | 5 (33) | 84 (17) | |
| *For the first time sexual intercourse* | | | | |
| 18 or younger | 18 (72) | 6 (40) | 296 (58) | 0.14 |
| 19 or older/never | 7 (28) | 9 (60) | 210 (42) | |
| **Social development** | | | | |
| *At least one year of membership in a sports club, primary school* | | | | |
| Yes | 20 (80) | 9 (60) | 427 (84) | 0.04** |
| No | 5 (20) | 6 (40) | 80 (16) | |
| *Number of friends in first-third grade, primary school* | | | | |
| < 4 | 8 (32) | 6 (40) | 187 (37) | 0.85 |
| ≥ 4 | 17 (68) | 9 (60) | 319 (63) | |
| *Number of friends in fourth-sixth grade, primary school* | | | | |
| < 4 | 7 (28) | 6 (40) | 156 (31) | 0.71 |
| ≥ 4 | 18 (72) | 9 (60) | 349 (69) | |
| *Best friend, primary school* | | | | |
| Yes | 22 (88) | 11 (73) | 377 (74) | 0.30 |
| No | 3 (12) | 4 (27) | 131 (26) | |
| *Most of the time playing with ... , primary school* | | | | |
| Friends | 22 (92) | 13 (87) | 436 (88) | 0.83 |
| Brothers, and/or sisters, parents, on your own | 2 (8) | 2 (13) | 62 (12) | |
| *Member sports club, secondary school* | | | | |
| Yes | 18 (72) | 9 (60) | 373 (74) | 0.50 |
| No | 7 (28) | 6 (40) | 134 (26) | |
| *Number of friends, secondary school* | | | | |
| < 4 | 4 (17) | 3 (20) | 154 (30) | 0.25 |
| ≥ 4 | 20 (83) | 12 (80) | 352 (70) | |
| *Best friend, secondary school* | | | | |
| Yes | 22 (92) | 10 (67) | 372 (74) | 0.11 |
| No | 2 (8) | 5 (33) | 134 (26) | |
| *Belonging to a group of friends, secondary school* | | | | |
| Yes | 21 (87) | 9 (60) | 403 (81) | 0.09 |
| No | 3 (13) | 6 (40) | 97 (19) | |

**Table 3,** continued

| | | | | |
|---|---|---|---|---|
| *Leisure time, mainly with ... , secondary school* | | | | |
| Friends | 22 (92) | 12 (80) | 430 (85) | 0.57 |
| Brothers/sisters/parents | 2 (8) | 3 (20) | 75 (15) | |
| *Going out to a bar or disco, secondary school* | | | | |
| Sometimes/often | 18 (72) | 10 (67) | 430 (85) | 0.05 |
| Never | 7 (28) | 5 (33) | 77 (15) | |
| *Member sports club, after secondary school* | | | | |
| Yes | 13 (52) | 6 (40) | 243 (49) | 0.75 |
| No | 12 (48) | 9 (60) | 254 (51) | |

The sums of each milestone may be less than the total of patients due to missing data. Chi square test or Fisher's exact test used as appropriate.

* Significant difference between BA OLT vs. reference (p=0.01).

** Significant difference between BA OLT vs. reference (p=0.01).

*Risk behavior, item level*

Comparison of items of the two risk behavior subscales (antisocial behavior and substance use and gambling) showed eight differences (Table 4). More non-transplanted BA patients had been suspended from secondary school because of misbehavior compared to the reference group (p=0.01) and the transplanted group (p=0.01). Transplanted BA patients drank significantly less often alcohol at secondary school compared to the reference group (p=0.01). Both the non-transplanted and transplanted BA patients drank less often alcohol after secondary school compared to the reference group. At secondary school, non-transplanted BA patients gambled less often than the reference group (p=0.02), and both the transplanted and non-transplanted BA patients gambled less often than the reference group after secondary school (both p=0.01).



**Table 4:** Risk behavior in adult BA patients with native liver or after liver transplantation and in a reference group, and comparison of the study groups. Data depict absolute number (percentage).

| | BA native liver n=25 | BA OLT n=15 | Reference group n=508 | P-value difference between groups |
|---|---|---|---|---|
| **Antisocial behavior** | | | | |
| *Ever been suspended because of misbehavior at school, primary school* | | | | |
| Yes | 2 (8) | 0 (0) | 35 (7) | 0.55 |
| No | 22 (92) | 15 (100) | 473 (93) | |
| *Got into trouble with the police or law, secondary school* | | | | |
| Yes | 3 (12) | 2 (13) | 84 (17) | 0.79 |
| No | 22 (88) | 13 (87) | 423 (83) | |

**Table 4**, continued

| | | | | | |
|---|---|---|---|---|---|
| *Ever been suspended because of misbehavior at school, secondary school* | | | | | |
| | Yes | 8 (32) | 0 (0) | 66 (13) | 0.01* |
| | No | 17 (68) | 15 (100) | 441 (87) | |
| *Ever been refused to lessons, secondary school* | | | | | |
| | Yes | 12 (48) | 4 (27) | 174 (34) | 0.30 |
| | No | 13 (52) | 11 (73) | 333 (66) | |
| **Substance use and gambling** | | | | | |
| *Alcohol, secondary school* | | | | | |
| | Often/very often | 3 (12) | 0 (0) | 138 (27) | 0.02** |
| | Never/occasionally | 22 (88) | 14 (100) | 368 (73) | |
| *Smoking, secondary school* | | | | | |
| | Yes | 8 (32) | 5 (33) | 201 (40) | 0.92 |
| | No | 17 (68) | 10 (67) | 363 (60) | |
| *Soft drugs, secondary school* | | | | | |
| | Occasionally/ often/very often | 7 (28) | 4 (27) | 149 (29) | 0.96 |
| | Never | 18 (72) | 11 (73) | 357 (71) | |
| *Psychedelic drugs, secondary school* | | | | | |
| | Occasionally/ often/very often | 2 (8) | 0 (0) | 19 (4) | 0.41 |
| | Never | 23 (92) | 15 (100) | 488 (96) | |
| *Hard drugs, secondary school* | | | | | |
| | Occasionally/ often/very often | 2 (8) | 0 (0) | 10 (2) | 0.11 |
| | Never | 23 (92) | 15 (100) | 497 (98) | |
| *Gambling, secondary school* | | | | | |
| | Occasionally/ often/very often | 1 (4) | 1 (7) | 112 (22) | 0.04*** |
| | Never | 24 (96) | 14 (93) | 393 (78) | |
| *Alcohol, after secondary school* | | | | | |
| | Often/very often | 4 (16) | 0 (0) | 246 (50) | 0.00# |
| | Never/occasionally | 21 (84) | 15 (100) | 245 (50) | |
| *Smoking, after secondary school* | | | | | |
| | Yes | 10 (40) | 3 (20) | 238 (48) | 0.08 |
| | No | 15 (60) | 12 (80) | 258 (52) | |

**Table 4**, continued

| | | | | | |
|---|---|---|---|---|---|
| *Soft drugs, after secondary school* | | | | | |
| | Occasionally/ often/very often | 10 (40) | 3 (20) | 145 (29) | 0.37 |
| | Never | 15 (60) | 12 (80) | 352 (71) | |
| *Psychedelic drugs, after secondary school* | | | | | |
| | Occasionally/ often/very often | 2 (8) | 1 (7) | 43 (9) | 0.96 |
| | Never | 23 (92) | 14 (93) | 456 (91) | |
| *Hard drugs, after secondary school* | | | | | |
| | Occasionally/ often/very often | 3 (12) | 1 (7) | 33 (7) | 0.58 |
| | Never | 22 (88) | 14 (93) | 466 (93) | |
| *Gambling, after secondary school* | | | | | |
| | Occasionally/ often/very often | 4 (16) | 1 (7) | 190 (38) | 0.01## |
| | Never | 21 (84) | 13 (93) | 308 (62) | |

The sums of each milestone may be less than the total of patients due to missing data.

* Significant difference between BA native liver vs. reference (p=0.01) and BA native liver vs. BA OLT (p=0.01).

** Significant difference between BA OLT vs. reference (p=0.01).

*** Significant difference between BA native liver vs. reference (p=0.02).

# Significant differences between BA native liver vs. reference (p=0.00) and BA OLT vs. reference (p=0.00).

## Significant differences between BA native liver vs. reference (p=0.01) and BA OLT vs. reference (p=0.01).



*Other factors*

No significant differences were found for living with parents, marital status, educational level, or employment status between the three groups (Table 5).

**Table 5:** living situation, educational level, marital and employment status in adult BA patients with native liver or after liver transplantation and a reference group, and comparison of the BA groups with the reference group. Data depict absolute number (percentage).

| | BA native liver n = 25 | BA OLT n = 15 | Reference group n = 508 | P-value difference between groups |
|---|---|---|---|---|
| *Living with their parents* | | | | |
| No | 13 (52) | 7 (47) | 328 (65) | 0.17 |
| Yes | 12 (48) | 8 (53) | 180 (35) | |
| *Marital status* | | | | |
| Married/living together | 7 (28) | 5 (33) | 192 (39) | 0.49 |
| Single | 18 (72) | 10 (67) | 299 (61) | |
| *Educational level* | | | | |
| Low | 6 (25) | 5 (36) | 143 (29) | 0.59 |
| Middle | 15 (63) | 5 (36) | 246 (51) | |
| High | 3 (12) | 4 (27) | 97 (20) | |
| *Employment status* | | | | |
| Employed | 12 (96) | 7 (93) | 295 (93) | 0.87 |
| Student | 11 | 6 | | |
| Not employed | 1 (4) | 1 (7) | 22 (7) | |



## DISCUSSION

To our knowledge, this is the first study examining course of life (COL) in a nationwide cohort of young-adult patients who had been diagnosed with BA in infancy. It is not only important to gain knowledge on the medical status of BA patients, but also on the psychosocial consequences since BA is often considered to be a chronic disease. In general, the present study shows that BA patients seem to reach developmental milestones equally well as young individuals not confronted with a serious physical condition. The only significant difference on subscale level is in risk behavior. Transplanted BA patients reported less substance use and gambling than the reference group.

While on subscale level non-transplanted and transplanted BA patients seem to reach developmental milestones at the same age as the reference group, on item level two differences were found. Transplanted patients were older at the time they had their first girlfriend/boyfriend and fewer were member of a sports club at primary school.

On item level, to our surprise, patients surviving BA into adulthood with native liver reported increased risk behavior. These patients were suspended more often because of misbehavior at secondary school as compared to the reference group. Furthermore, it is noteworthy that there is no difference between patients with BA and the general population in use of alcohol at secondary school. This is a rather worrisome finding since BA is a chronic liver disease that often ends in liver transplantation. Therefore, one would expect that alcohol use in BA patients is lower compared to

the reference group. This risk behavior of the non-transplanted group could be the consequence of the limitations posed by their disease in early childhood. In this line of reasoning, the increased risk behavior can be seen as compensatory.[165] Previous studies on this matter concerning smoking in survivors of cancer are equivocal. Some report that children surviving from cancer are less likely to start smoking, but once having started, are at similar risk for becoming persistent smokers as controls.[61,175] Others report that smoking habits of children surviving cancer were comparable with the general population.[65,194]

After secondary school, non-transplanted BA patients did use significantly less alcohol compared to the reference group. Transplanted BA patients used significantly less alcohol during secondary school and after secondary school compared to the reference group. It is common practice in our country to advise against regular alcohol consumption in patients with chronic liver disease. Transplanted BA patients seem to behave more conform this advise than the non-transplanted patients. Furthermore, non-transplanted BA patients were less likely to gamble at secondary school, and both non-transplanted and transplanted BA patients were less likely to gamble after secondary school compared to the reference group.

Based on our results we have to reject our hypothesis that transplanted and non-transplanted BA survivors have a delayed COL compared to the reference group. No significant differences were found on subscale level between the two groups and the reference group, except in decreased substance use and gambling in the transplanted BA patients.

BA is a chronic disease for which major surgery is necessary and patients need a life lasting follow-up. Young adults surviving BA into adulthood with native liver seem to fare better when compared to young adults having been confronted with other pediatric diseases, such as childhood cancer or other congenital diseases such as anorectal malformations or Hirschsprung's disease.[166]

In esophageal atresia gastrointestinal continuity can be restored shortly after birth, but this does not ensure normal functioning.[165,166] If treated in time this is not a life-threatening disease, as opposed to BA. In contrast to the children with other conditions, in BA patients no significant differences with the reference group were found on the COL developmental subscales. We do not have a clear explanation for this finding. As described above, BA patients may also be admitted to hospital for complications such as cholangitis or cirrhosis associated complications such as oesophageal varices bleeding.[103] It can be assumed that BA patients reaching adulthood without OLT have a relatively benign course of their disease and are therefore less likely delayed in COL. Furthermore, a fifth of patients surviving BA without OLT have normal liver biochemistry up to twenty years and have no clinical or ultrasonographic signs of liver cirrhosis.[34,103] A benign course of disease could partly explain the results of the current study since the remaining 80% of non-transplanted BA survivors suffer mild to moderate disturbances in liver biochemistry. The transplanted patients had a worse course of disease culminating in life-threatening liver failure. It could be that a good clinical outcome after OLT, especially in very young children who do not remember the OLT, leads to a relatively undisturbed COL. This could even mean that these patients are less hampered in COL than non-transplanted BA patients. However, most transplanted patients are bound to life-lasting immunosuppression, which carries its own side effects and morbidity. Still, these groups report a COL that is comparable to that of the reference group.

This study has a few limitations. Because of the high mortality of BA patients, especially more than 20 years ago, and the low prevalence of BA, only 54 patients were eligible for this study. Despite a reasonably good response rate (74%) and a nationwide cohort spanning 15 years, the

eligible study population is relatively small. An international study will be necessary to make more firm statements about the COL of BA patients and possible differences between those living with their native liver and those living after OLT. A larger study population will mean more statistical power. Differences not significant in the present study may become revealed in a study with more power.

Our study could also be subject to recall bias, because it is a retrospective study. It is possible that the patients over- or underestimated their achievement of developmental milestones. However, the recall bias is expected to be similar in the reference group. A prospective study design would rule out this type of bias.

We recommend it could prove worthwhile to more actively discourage use of alcohol in non-transplanted patients at secondary school. A decreased use of alcohol in BA patients can be seen as adaptive behavior, especially in children with chronic liver disease. Transplanted BA patients seem to be well informed about the risks of alcohol in their situation. The results of the present study are rather reassuring for patients and their caregivers. Based on our results it is not necessary for physicians to have an extra focus on COL in developing children with BA, except on use of alcohol. An interesting subsequent research topic would be to investigate the age at which BA survivors reach their developmental milestones in comparison with a reference group. Longitudinal research in younger BA patients would be necessary to gain more insight in the age at which developmental milestones are achieved. Information about the quality of life of BA survivors would also be of value to inform parents about the prognosis of their child.