Cost-Effectiveness of Treatments in Children With Attention-Deficit/Hyperactivity Disorder: A Continuous-Time Markov Modeling Approach

Roel D. Freriks, Jochen O. Mierau, Jurjen van der Schans, Annabeth P. Groenman, Pieter J. Hoekstra, Maarten J. Postma, Erik Buskens, and Qi Cao

Abstract
Objectives. This study aimed to assess the cost-effectiveness of treatments for attention-deficit/hyperactivity disorder (ADHD) in children through prevention of serious delinquent behavior. Cost-effectiveness was assessed in net-monetary benefit (NMB). Methods. To evaluate the three major forms of ADHD treatment (medication management, behavioral treatment, and the combination thereof) relative to community-delivered treatment (control condition), we used data from 448 children, aged 7 to 10, who participated in the National Institute of Mental Health’s Multimodal Treatment Study of Children with ADHD. We developed a three-state continuous-time Markov model (no delinquency, minor to moderate delinquency, serious delinquency) to extrapolate the results 10 years beyond the 14-month trial period at a 3% discount rate. Serious delinquency was considered an absorbing state to enable assessment in life-years (LYs) of serious delinquent behavior prevented. The willingness-to-pay (WTP) threshold was set equal to the annual cost associated with serious delinquency in children with ADHD of $12,370. Results. Modeled and observed outcomes matched closely with a mean difference of 6.9% in LYs of serious delinquent behavior prevented. The economic evaluation revealed a NMB of $95,449, $88,553, $90,536 and $98,660 for medication management, behavioral treatment, combined treatment, and routine community care, respectively. Estimates remained stable after linearly increasing the WTP threshold between $0 and $50,000 in the deterministic sensitivity analyses. Conclusions. This study assessed the cost-effectiveness of treatments for ADHD in children using continuous-time Markov modeling. We show that treatment evaluation in broader societal outcomes is essential for policy makers, as the three major forms of ADHD treatment turned out to be inferior to the control condition.

Keywords
attention-deficit/hyperactivity disorder, cost-effectiveness, continuous-time Markov modeling

Date received: June 24, 2018; accepted: July 5, 2019

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate and impairing inattention, hyperactivity, and impulsivity, mostly seen and diagnosed in children and adolescents. According to the most recent meta-analysis of Polanczyk et al. of 41 studies in 27 countries from every world region, the prevalence of ADHD in children and adolescents is estimated around 3.4%. Academic failure, poor self-esteem, troublesome peer and family relationships, substance abuse, and delinquent behavior are associated with ADHD, and patients are often diagnosed with one or more co-occurring
psychiatric disorders.\textsuperscript{1,2,4,5} The majority of children and adolescents diagnosed continue to have impairing symptoms into adulthood.\textsuperscript{1,2,5} The negative impact of ADHD within and beyond the health system during childhood and the long-lasting impact into adulthood result in significant long-term personal and societal costs.\textsuperscript{6–9}

The major treatments to mitigate the related (economic) burden of ADHD are medication management and behavioral treatment, alone or in combination.\textsuperscript{10} Jensen et al. evaluated the cost-effectiveness of these treatments using data from the National Institute of Mental Health’s (NIMH) Multimodal Treatment Study of Children with ADHD (MTA study),\textsuperscript{11} in which 579 children with ADHD were assigned to 14 months of controlled medication management, behavioral treatment, the combination of medication management, and behavioral treatment (also referred to as combined treatment), or routine community care (control condition).\textsuperscript{10–12} The cost-effectiveness of medication management proved superior to behavioral treatment at the end of the 14-month trial.\textsuperscript{11} The combined treatment is less superior than medication management due to the considerable increase in costs associated with behavioral treatment.\textsuperscript{11} We build on this study by focusing on the cost-effectiveness beyond the trial period of the MTA study. Hence, a decision model was developed to evaluate the 10-year cost-effectiveness of the treatments of the MTA study.

Contrary to previous Markov models for ADHD treatment evaluation,\textsuperscript{13–16} we propose a different model structure. First, ADHD is a chronic condition that makes a full remission state unlikely. Second, the level of ADHD symptoms tend to be highly persistent over time.\textsuperscript{17,18} Thus, decision models with diseases states based on ADHD symptoms end up with extremely low or high transition probabilities, which limits the applicability of the model. Third, treatments for ADHD are mostly evaluated in terms of symptomatic outcomes, while the (economic) burden of ADHD often extends to society at large.\textsuperscript{6–9} For example, antisocial behaviors and delinquency associated with ADHD result in significant costs for society.\textsuperscript{19–21} Specifically, D’Amico et al. demonstrated that conduct disorders in childhood are associated with a two- to threefold increase in early adulthood costs, mainly driven by criminal acts and judicial contacts.\textsuperscript{22} Therefore, we defined delinquency states for our decision model. Importantly, delinquency is a distinct indicator for children’s behavior and partaking in society. Also, robust correlations between delinquency and the level of ADHD symptoms are found in the literature.\textsuperscript{23–25} Fourth, we followed common practice and based the extrapolation on data within the trial period of the MTA study. Subsequently, contrarily to previous studies, we used follow-up data to assess the accuracy of the model’s long-term prediction to ensure reliability of modeling estimates in future economic evaluation. Finally, the previous Markov models for ADHD treatment evaluation consider discrete time periods.\textsuperscript{13–16} Consequently, changes in states occur only at the beginning or end of predefined time intervals.\textsuperscript{26} We have relaxed this assumption to build our model in continuous time. This relaxation was previously shown to result in more accurate estimates.\textsuperscript{27}

Methods

NIMH’s Multimodal Treatment Study of Children With ADHD (MTA Study)

For this study, we used data from the MTA study, a multi-site randomized controlled trial that was conducted in the United States and was designed to evaluate the major forms of ADHD treatment.\textsuperscript{10,12} Children had been randomly assigned to one of the three active treatments—medication management, behavioral treatment, or the combination thereof (hereafter combined treatment)—or routine community care. Routine community care is the control condition and reflects the nature of less intensive (and less costly) community-
delivered treatment. The MTA study involved 14 months of controlled treatment in 579 children with ADHD, aged 7 to 10 years, with naturalistic follow-ups for up to 16 years after the end of the trial period. Follow-up assessments were carried out during childhood (2 and 3 years after baseline), (late-)adolescence (6, 8, and 10 years after baseline), and adulthood (12, 14, and 16 years after baseline). We used the follow-up data of childhood and late-adolescence periods, since our modeled outcome variable (delinquency) was not assessed in adulthood. Summary statistics of the baseline characteristics age, gender, comorbidity, intelligence, ethnic background, and occupation-based socioeconomic family status are presented in Table 1.

Comorbidity is a dummy variable that equals 1 for the presence of anxiety and/or depression. Intelligence is the child’s total intelligence quotient (IQ) measured with the Wechsler Intelligence Scale for Children–III (WISC-III). Ethnic background is a dummy variable that equals 1 for children from a non-Caucasian background. Finally, occupation-based socioeconomic family status is a dummy variable that equals 1 for children from a high socioeconomic family status. Further details on the four treatment modes of the MTA study and other baseline characteristics are available in previous publications.10,12,28,29 All study procedures had been approved by institutional review boards and were carried out in accordance with the Declaration of Helsinki. Participants and parents were informed of the procedures and provided written informed consent.10

| Table 1 Baseline Characteristics of the Dropped and Selected Samplea |
|---------------------------------------------------------------|
|                                      | Dropped Sample (N = 131) | Selected Sample (N = 448) |
| Age (SD)             | 7.90 (0.84)               | 7.74 (0.80)*               |
| Female               | 16.79%                    | 20.54%                     |
| Comorbidity          | 25.95%                    | 25.22%                     |
| Intelligence, WISC-III IQ (SD) | 102.06 (13.08)          | 100.16 (15.22)            |
| Non-Caucasian background | 37.40%                    | 39.19%                     |
| High occupation-based socioeconomic family status | 29.77% | 31.70% |

IQ, intelligence quotient; SD, standard deviation; WISC, Wechsler Intelligence Scale for Children.

aInference: * indicate significant differences at the 5%/1% level based on the mean differences of the two samples, assessed with a t test.

Delinquency
In this study, a six-point scale on delinquency was used as primary outcome variable,29 coded ordinally from two parent-report measures, the DISC-IV-CD Module and the Parent DSM-IV Aggression and Conduct Disorder Rating Scale,30 and two self-report measures. Specifically, the Self-Reported Antisocial Behavior questionnaire31 at the 2-year assessment and the Self-Reported Delinquency questionnaire32 at the 3-year assessment. By using all available procedures participants were assigned (retrospectively) a delinquency classification code at each assessment point.33–36 The coding scheme of the Pittsburg Youth Study was used to contribute items to each code.35,36

The delinquency scale was then categorized as follows: 0 = no delinquency; 1 = minor delinquency only at home (e.g., theft of less than $5 or vandalism); 2 = minor delinquency outside of the home (e.g., vandalism, cheating someone, shoplifting less than $5); 3 = moderately serious delinquency (e.g., vandalism, theft of $5 or more, carrying a weapon); 4 = serious delinquency (e.g., breaking and entering, drug selling, attacking someone with the intent to seriously hurt or kill, rape); 5 = engagement in two or more different level 4 offences. This variable was assessed at baseline, after the 14-month trial period, and at the follow-up assessments after 2, 3, 6, and 8 years.

Markov Model
To predict the trajectories of delinquent behavior during adolescence in relation to the four treatment modes of the MTA study, we developed a continuous-time Markov model26 based on three delinquency states (Figure 1): no delinquency (state 1), minor to moderate delinquency (state 2), and serious delinquency (state 3). The states were discerned based on the delinquency scale mentioned above, in which a 0 score was considered no delinquency, 1 to 3 scores minor to moderate delinquency, and scores 4 and 5 were considered serious delinquency.

The specification, parameter estimation, and evaluation of this model were conducted using vertical modeling formulation37 based on a previously suggested framework.38 Briefly, this includes the specification of the Markov process by means of two main parameters: 1) sojourn time distributions and 2) the probabilities of the next state visited (also referred to as the future state probabilities). The estimation of the parameters are subsequently conducted in which the treatment indicator
can easily be incorporated in the corresponding parametric survival and multinomial regression models. Finally, the modeled outcomes can be evaluated using Monte-Carlo simulation of the whole procedure.

To assess the cost-effectiveness of the treatments through prevention of serious delinquent behavior, we considered serious delinquency to be an absorbing state. This assumption does not allow participants to either make transition out of this state (i.e., decrease the delinquency level after entering the serious delinquency state) or start in this state (i.e., enrolling in this study with delinquency levels 4 or 5). Consequently, within the total sample size of 579 children, our Markov model was built based on the delinquency data from 448 children. The reason for exclusion of these 131 children was that they either already had a 4 or 5 delinquency score when enrolling in the study or follow-up data was missing.

Exponential survival models were subsequently used to estimate the cumulative distribution functions of the sojourn time in both states 1 and 2 \((F_i(u), i = 1, 2)\). The future state probabilities \((\pi_{ij}, i = 1, 2; j = 1, 2, 3; i \neq j)\) were estimated by fitting logistic regression models to the event indicator of entering the serious delinquency state from the no delinquency state \(\pi_{13}\) and from the minor to moderate delinquency state \(\pi_{23}\). The transition probabilities between the no delinquency state and minor to moderate delinquency state can then be calculated using one minus the two previously mentioned two probabilities. The treatment indicator was incorporated as the covariate in both exponential survival models and the logistic regression models.

We developed our model based on the individual trajectory of delinquency seriousness within the trial period, as we use the 10-year follow-up data to validate accuracy of long-term prediction. The outcome of our model is the average time of not reaching the serious delinquency state, defined the same as the life-years (LYs) of serious delinquent behavior prevented. Model performance was subsequently internally validated by comparing the predicted (average across 100,000 simulation runs) probability of serious delinquent behavior prevented (based on Kaplan-Meier estimate) to the observed empirical survival curves with the same outcome variable. The simulated results reflected a 10-year time horizon. The available follow-up data in the MTA study enables the unique opportunity to internally validate the modeling prediction at 10-year follow-up for the four different treatments.

**Economic Evaluation**

We included treatment costs in which the following three components were taken into account: medication cost, visit cost for teachers and aides, and cost of psychiatrist, psychologist, and pediatrician. Per treatment group, we converted the longitudinal costs into daily costs. The respective resulting daily costs were $0.52 for routine community care, $0.62 for medication management, $3.18 for behavioral treatment, and $3.53 for the combined treatment. Total treatment costs were calculated by multiplying the LYs of serious delinquent behavior prevented and the daily costs. The annual rate of discounting was set at 3% for both cost and effectiveness outcomes. We compared the cost-effectiveness outcomes among the treatments in terms of a net-monetary benefit (NMB) framework. The willingness-to-pay (WTP) threshold was set equal to the annual cost associated with serious juvenile delinquency in children with ADHD retrieved from previous research in the United States. Specifically, criminal history was assessed through self-report, including crimes, juvenile detention, probation, and jail. The costs of crimes incurred by victims and costs to the criminal justice system were estimated based on information from the Bureau of Justice Statistics, the Federal Bureau of Investigation, and the Criminal Justice Institute. The mean total criminal costs were $12,868 and $498 for children with and without ADHD, respectively. Hence, we incorporated the adjusted difference of $12,370 as WTP threshold. As such, we incorporated the cost avoided in the serious delinquency state in the economic evaluation. The cost-effectiveness can then easily be calculated within this framework as follows:

![Figure 1 Schematic Representation of the Markov Model.](image-url)
NMB = mean prevented LYs × WTP
− mean total treatment cost

\[ NMB = \text{mean prevented LYs} \times \text{WTP} - \text{mean total treatment cost} \] (1)

The WTP threshold is a key parameter for the NMB analysis, hence determining the conclusions drawn from the economic evaluation. Therefore, we reevaluated Equation (1) in deterministic sensitivity analyses with linearly increasing WTP thresholds between $0 and $50,000.

### Further Analyses

We used logistic regression models to control for sample selection and the likelihood of absorbance. In the first model, we controlled for the effect of sample selection by estimating odds ratios (ORs) of model exclusion conditional on the relevant covariates age, gender, comorbidity, intelligence, ethnic background, and occupation-based socioeconomic family status. We established whether the covariates mentioned above were independent predictors for model exclusion at a 5% significance level. In the second model, we focused on the likelihood of the absorbance in the serious delinquency state. We compared the adjusted OR of absorbance in the serious delinquency state with moving out of this state at a 5% significance level for both the included and excluded children. All of above statistical analyses were performed with R 3.2.4 (R Foundation; https://www.r-project.org/foundation/) and STATA/SE 15.0 (STATA; https://www.stata.com/).

### Results

#### Model Validation

The model parameter estimation results are presented in Table 2. As is shown in Figure 2, the predicted survival curves obtained from our Markov model closely resembled the observed survival curves. The only exception was the curve for children who were assigned to medication management, in which a clear overestimation of the probability of preventing serious delinquent behavior was detected. Our model provided excellent predictions for children assigned to routine community care and the combined strategy of medication management and behavioral treatment. Specifically, the mean difference in percentage of LYs of serious delinquent behavior prevented between the modeled and observed trajectories is 8.5% for medication management, 7.8% for behavioral treatment, 5.8% for the combined treatment, and 5.7% for routine community care.

### Table 2 The Specification and the Results of the Parameter Estimation for the Markov Model\(^a\)

| Markov Model | \(\alpha\) | \(\beta_{T}\) |
|--------------|----------|-----------|
| \(F_1(u)\)   |          |           |
| T1           | 6.89 (0.22) | 0.08 (0.32) |
| T2           | 6.89 (0.22) | 0.13 (0.32) |
| T3           | 6.89 (0.22) | -0.10 (0.30) |
| T4           | 6.89 (0.22) | -0.15 (0.22) |
| \(F_2(u)\)   |          |           |
| T1           | 7.01 (0.17) | -0.16 (0.22) |
| T2           | 7.01 (0.17) | -0.02 (0.24) |
| T3           | 7.01 (0.17) | -0.01 (0.22) |
| T4           | 7.01 (0.17) | -0.01 (0.22) |
| \(\pi_{13}\) |          |           |
| T1           | -3.13 (1.10) | 0.61 (1.25) |
| T2           | -3.13 (1.10) | 0.64 (1.25) |
| T3           | -3.13 (1.10) | 0.64 (1.25) |
| T4           | -3.13 (1.10) | 0.07 (1.44) |
| \(\pi_{23}\) |          |           |
| T1           | -3.13 (0.67) | 0.20 (0.49) |
| T2           | -3.13 (0.67) | 0.23 (0.50) |
| T3           | -3.13 (0.67) | 0.23 (0.50) |
| T4           | -3.13 (0.67) | -0.33 (0.54) |

\(^a\)Standard errors in parentheses; T2, T3, T4, respectively, represent routine community care, medication management, behavioral treatment and combined treatment, with routine community care as the reference category for \(\beta_{T}\); \(\theta(\pi) = \log(p/(1 - p))\) is the logit function.
Figure 2  Results of the model validation for the four treatment modes: (a) routine community care, (b) medication management, (c) behavioral treatment, (d) combined treatment; straight lines represent observed data, and dashed lines represent the model prediction.
Economic Evaluation

Thirty-two of the 448 children (7%), who started at baseline in the no delinquency or mild to moderate delinquency state, reached the serious delinquency state within 10 years. For policy makers this is a substantial percentage, looking at the description of the delinquency levels associated with this state and taking into account the annual cost associated with serious juvenile delinquency in children with ADHD of $12,370.6 Table 3 presents the cost-effectiveness results stratified by the four treatment modes considered in the MTA study. We performed both undiscounted and discounted analyses.

Table 3 Results of the Economic Evaluation Stratified by Treatment Mode

| Treatment Mode           | Mean Total Cost ($) | Mean LYs Prevented (Years) | Mean NMB ($) |
|--------------------------|---------------------|---------------------------|--------------|
| Undiscounted             |                     |                           |              |
| a. Routine community care| 1,769               | 9.32                      | 113,519      |
| b. Medication management | 2,043               | 9.03                      | 109,658      |
| c. Behavioral treatment  | 10,539              | 9.08                      | 101,781      |
| d. Combined treatment    | 12,111              | 9.40                      | 104,167      |
| Discounted               |                     |                           |              |
| a. Routine community care| 1,537               | 8.10                      | 98,660       |
| b. Medication management | 1,779               | 7.86                      | 95,449       |
| c. Behavioral treatment  | 9,170               | 7.90                      | 88,553       |
| d. Combined treatment    | 10,527              | 8.17                      | 90,536       |

LY, life-year; NMB, net monetary benefit.

Figure 3 NMB plot with linearly increasing WTP thresholds between $0 and $50,000.

In 10 years time, the discounted average LYs of serious delinquent behavior prevented were 7.86 for medication management, 7.90 for behavioral treatment, 8.17 for the combined treatment, and 8.10 for routine community care. Although the combined treatment had the highest LYs prevented, routine community care turned out to be the optimal strategy in terms of cost-effectiveness with the highest mean NMB due to the substantial difference in treatment cost.

Figure 3 illustrates that the difference in NMB between routine community care and the two active treatments medication management and behavioral treatment increases as
the WTP increases, while the difference in NMB between routine community care and the combined treatment reduces. The latter is due to the fact that the difference in treatments cost becomes, relatively, less determinative for the NMB results.

**Further Analyses**

Table 4 demonstrates that the results are not driven by sample selection, as none of the ORs of model exclusion conditional on the relevant covariates age, gender, comorbidity, intelligence, ethnic background, or occupation-based socioeconomic family status were statistically significant at a 5% level.

Furthermore, we determined the likelihood of absorbance in the serious delinquency state once a child entered this state. We found for the 448 included children an adjusted OR of continuation in the serious delinquency state of 1.471 ($P < 0.001$), against an adjusted OR of moving out the serious delinquency state of $-1.423$ ($P < 0.001$). Similarly, we found for the 131 excluded children an adjusted OR of continuation in the serious delinquency state of 0.927 ($P < 0.001$), against an adjusted OR of moving out the serious delinquency state of $-0.953$ ($P < 0.001$). Hence, the serious delinquency state is more likely absorbent than transient for both groups.

**Discussion**

In this study we assessed the long-term cost-effectiveness of the three major forms of ADHD treatment and routine community care beyond the 14-month trial period of the MTA study. For this we developed a Markov model with an innovative model structure. We considered the high-cost serious delinquency state to be absorbing to predict the LYs of serious delinquent behavior prevented over a time period of 10 years. The availability of long-term follow-up data in the MTA study enabled us to assess the accuracy of modeling prediction. Modeled and observed outcomes matched closely with a mean difference of 6.9%. Hence, the model delivers reliable estimates when used in future economic evaluations. By setting the WTP equal to the cost avoided in the serious delinquency state, we calculated cost-effectiveness in terms of NMB. Results of the economic evaluation revealed that the combined treatment was the only active treatment mode that further decreases serious delinquent behavior compared with routine community care. However, the substantial difference in treatment cost renders the routine community care to be the optimal treatment strategy in terms of NMB. Moreover, results are robust to manipulating the WTP threshold in deterministic sensitivity analyses.

These findings are in line with previous research with the MTA study. Molina et al. demonstrated that while after 3 years the active ADHD treatments had improved symptomatic symptoms of the children relative to the control condition, no differences were found with respect to delinquent behavior. Although the MTA study was not originally designed to examine delinquency, we argue that it is interesting for policy makers to see whether the pursued medical effects of the treatments translate into positive effects with respect to behavior of these children in society. Clearly, the economic impact of ADHD often extends to society beyond the health system and treatment effects on ADHD symptoms and broader societal aspects of the disorder differ substantially. Additionally, Schawo et al. plead for model-based studies in ADHD using empirical data for model validation and broader societal outcomes as the modeled outcome. As such, the evaluation form in this study has its potential to be extended to a broader perspective.

Table 4

| Model Exclusion Indicator | Odds Ratios | Marginal Effects |
|---------------------------|-------------|-----------------|
| Age                       | -0.232 (0.1237) | -0.041 (0.0214) |
| Female                    | 0.266 (0.2607)  | 0.046 (0.0454)  |
| Comorbidity               | -0.083 (0.2301) | -0.014 (0.0401) |
| Intelligence, WISC-III IQ | -0.007 (0.0076) | -0.0012 (0.0013) |
| Non-Caucasian background  | 0.090 (0.2109)  | 0.016 (0.0368)  |
| High occupation-based socioeconomic family status | 0.094 (0.2224) | 0.016 (0.0388) |

IQ, intelligence quotient; WISC, Wechsler Intelligence Scale for Children.
enables model validation according to the guidelines for simulating a continuous-time Markov model. Without including an absorbing state, the simulation along with our vertical modeling approach reaches an endless process. The only reason for a process to end is when the processing time is beyond our study time horizon of 10 years. Furthermore, with this model structure we were able to evaluate the treatments of the MTA study through prevention of serious delinquent behavior. The latter is highly relevant for policy makers as serious delinquency is associated with substantial societal cost. A limitation of this assumption is that we had to delete 22.6% of the original sample. However, we demonstrated that this assumption did not affect the modeled outcomes, as model exclusion was not predicted by the relevant child and family characteristics of age, gender, comorbidity, intelligence, ethnic background, and occupation-based socioeconomic family status. Moreover, results revealed that the serious delinquency state is more likely absorbent than transient for both included and excluded children.

In this study we included additional covariates to control the sensitivity of our modeling assumptions. Exploring the effect of these child and family characteristics on juvenile delinquency in children with ADHD is beyond the scope of this study, but remains an interesting topic for further research.

**Conclusions**

This study assessed the cost-effectiveness of treatments for ADHD in children using a continuous-time Markov model. The structure of the model allowed to evaluate the treatments through prevention of serious delinquent behavior over a time period of 10 years. The three major forms of ADHD treatment had a lower NMB than routine community care, which confirms the necessity for policy makers to evaluate ADHD treatments in broader societal outcomes before implementation.

**ORCID iD**

Roel D. Freriks https://orcid.org/0000-0002-9458-1832

**References**

1. Faraone SV, Asherson P, Banaschewski T, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1:15020.
2. Feldman HD, Reiff MI. Attention deficit-hyperactivity disorder in children and adolescents. *N Engl J Med*. 2014;370(9):838-46.
3. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry*. 2015;56(3):345-5.
4. Currie J, Stabile M. Child mental health and human capital accumulation: the case of ADHD. *J Health Econ*. 2006;25(6):1094-118.
5. Currie J, Stabile M, Manivong P, Roos LL. Child health and young adult outcomes. *J Hum Resour*. 2010;45(3):517-48.
6. Matza LS, Paramore C, Prasad M. A review of the economic burden of ADHD. *Cost Eff Resour Alloc*. 2005;3:5-13.
7. Hakkarta-van Roijen L, Zwis BW, Bouwmans C, et al. Societal costs and quality of life of children suffering from attention deficient hyperactivity disorder (ADHD). *Eur Child Adolesc Psychiatry*. 2007;16(5):316-26.
8. Doshi JA, Hodgkins P, Kahle J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):990-1002.
9. Le HH, Hodgkins P, Postma MJ, et al. Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. *Eur Child Adolesc Psychiatry*. 2014;23(7):587-98.
10. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/ hyperactivity disorder. Multimodal Treatment Study of Children with ADHD. *Arch Gen Psychiatry*. 1999;56(12):1073-86.
11. Jensen, P. S., Garcia, J. A., Glied, S., Crowe, M., Foster, M., Schlander, M., ... & Hechtman, L. Cost-effectiveness of ADHD treatments: findings from the multimodal treatment study of children with ADHD. *American Journal of Psychiatry*. 2005;162(9):1628-36.
12. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: changes in effectiveness and growth after the end of treatment. *Pediatrics*. 2004;113(4):762-9.
13. Faber A, van Agthoven M, Kalverdijk LJ, et al. Long-acting methylphenidate-OROS in youths with attention-deficit/hyperactivity disorder suboptimally controlled with immediate-release methylphenidate: a study of cost effectiveness in the Netherlands. *CNS Drugs*. 2008;22(2):157-70.
14. Wu EQ, Hodgkins P, Ben-Hamadi R, et al. Cost-effectiveness of pharmacotherapies for attention-deficit hyperactivity disorder: a systematic literature review. *CNS Drugs*. 2012;26(7):581-600.
15. Schawo S, Van der Kolk A, Bouwmans C, et al. Probabilistic Markov model estimating cost-effectiveness of methylphenidate osmotic-release oral system versus immediate-release methylphenidate in children and adolescents: which information is needed? *Pharmacoeconomics*. 2015;33(5):489-509.
16. van der Schans J, Kotsopoulos N, Hoekstra PJ, Hak E, Postma MJ. Cost-effectiveness of extended-release methylphenidate in children and adolescents with attention-deficit/hyperactivity disorder sub-optimally treated with...
immediate release methylphenidate. *PLoS One*. 2015;10(5):e0127237.

17. Asherson P, Buitelaar JK, Faraone SV, Rohde LA. Adult attention-deficit hyperactivity disorder: key conceptual issues. *Lancet Psychiatry*. 2016;3(6):568–78.

18. van Lieshout M, Luman M, Twisk JW, et al. A 6-year follow-up of a large European cohort of children with attention-deficit/hyperactivity disorder-combined subtype: outcomes in late adolescence and young adulthood. *Eur Child Adolesc Psychiatry*. 2016;25(9):1007–17.

19. Swensen AR, Birnbaum HG, Secnik K, Marynchenko M, Greenberg P, Claxton A. Attention-deficit/hyperactivity disorder: increased costs for patients and their families. *J Am Acad Child Adolesc Psychiatry*. 2003;42(12):1415–23.

20. Swensen AR, Birnbaum HG, Ben Hamadi R, Greenberg P, Cremieux PY, Secnik K. Incidence and costs of accidents among attention-deficit/hyperactivity disorder patients. *J Adolesc Health*. 2004;35(4):346.e1–e9.

21. Jones DE, Foster EM; Conduct Problems Prevention Research Group. Service use patterns for adolescents with ADHD and comorbid conduct disorder. *J Behav Health Serv Res*. 2009;36(4):436–49.

22. D’Amico F, Knapp M, Beecham J, Sandberg S, Taylor E, Sayal K. Use of services and associated costs for young adults with childhood hyperactivity/conduct problems: 20-year follow-up. *Br J Psychiatry*. 2014;204(6):441–7.

23. Barkley RA, Fischer M, Smallish L, Fletcher K. Young adult follow-up of hyperactive children: antisocial activities and drug use. *J Child Psychol Psychiatry*. 2004;45(2):195–211.

24. Jensen PS, Arnold LE, Swanson JM, et al. 3-year follow-up of the NIMH MTA study. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):989–1002.

25. Satterfield JH, Faller KJ, Crinella FM, Schell AM, Swanson JM, Homer LD. A 30-year prospective follow-up study of hyperactive boys with conduct problems: adult criminality. *J Am Acad Child Adolesc Psychiatry*. 2007;46(5):601–10.

26. van Rosmalen J, Toy M, O’Mahony JF. A mathematical approach for evaluating Markov models in continuous time without discrete-event simulation. *Med Decis Making*. 2013;33(6):767–79.

27. Soares MO, Canto E, Castro L. Continuous time simulation and discretized models for cost-effectiveness analysis. *Pharmacoeconomics*. 2012;30(12):1101–17.

28. Molina BS, Fiory K, Hinshaw SP, et al. Delinquent behavior and emerging substance use in the MTA at 36 months: prevalence, course, and treatment effects. *J Am Acad Child Adolesc Psychiatry*. 2007;46(8):1028–40.

29. Molina BSG, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(5):484–500.

30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington: American Psychiatric Association; 1994.

31. Loeber R, Stouthamer-Loeber M, Van Kammen WB, Farrington DP. Development of a new measure of self-reported antisocial behavior for young children: prevalence and reliability. In: Klein MW, ed. *Cross-National Research in Self-Reported Crime and Delinquency*. Boston: Kluwer; 1989. p 202–23.

32. Elliott DS, Huizinga D, Ageton SS. *Explaining Delinquency and Drug Use*. Beverly Hills: Sage; 1985.

33. Wolfgang ME, Figlio RM, Tracy PE, Singer SI. *The National Survey of Crime Severity*. Washington: US Government Printing Office; 1985.

34. Lee SS, Hinshaw SP. Severity of adolescent delinquency among boys with and without attention deficit hyperactivity disorder: predictions from early antisocial behavior and peer status. *J Clin Child Adolesc Psychol*. 2004;33(4):705–16.

35. Loeber R, Stouthamer-Loeber M, Van Kammen W, Farrington DP. Initiation, escalation and desistance in juvenile offending and their correlates. *J Criminal Law Criminology*. 1991;82(1):36–82.

36. Loeber R, Farrington DP, Stouthamer-Loeber M, van Kammen WB. *Antisocial Behavior and Mental Health Problems: Explanatory Factors in Childhood and Adolescence*. Mahwah: Lawrence Erlbaum; 1998.

37. Nicolaie MA, van Houwelingen HC, Putter H. Vertical modeling: a pattern mixture approach for competing risks modeling. *Stat Med*. 2010;29(11):1190–205.

38. Cao Q, Buskens E, Feenstra TL, Jaarsma T, Hillege H, Postmus D. Continuous-time semi-Markov models in health economic decision making: an illustrative example in heart failure disease management. *Med Decis Making*. 2016;36(1):59–71.

39. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: multivariate data analysis—choosing a model and assessing its adequacy and fit. *Br J Cancer*. 2003;89(4):605–11.

40. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.

41. Tambour M, Zethraeus N, Johannesson M. A note on confidence intervals in cost-effectiveness analysis. *Int J Technol Assess Health Care*. 1998;14(3):467–71.