

Modeled Economic Evaluation of Alternative Strategies to Reduce Sudden Cardiac Death Among Children Treated for Attention Deficit/Hyperactivity Disorder

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Background—Stimulants are widely used to treat children with attention deficit/hyperactivity disorder and may increase the risk for sudden cardiac death (SCD). We examined the cost-effectiveness of pretreatment screening with ECG for reducing SCD risk in children diagnosed with attention deficit/hyperactivity disorder who are candidates for stimulant medication.

Method and Results—We constructed a state-transition Markov model with 10 annual cycles spanning 7 to 17 years of age. Taking a societal perspective, we compared the cost-effectiveness of 3 screening strategies: (1) performing a history and physical examination with cardiology referral if abnormal (current standard of care); (2) performing a history and physical examination plus ECG after negative history and physical examination, with cardiology referral if either is abnormal; and (3) performing a history and physical examination plus ECG, with cardiology referral only if ECG is abnormal. Children identified with SCD-associated cardiac abnormalities would be restricted from stimulants and from playing competitive sports. The expected incremental cost-effectiveness over strategy 1 was \$39 300 and \$27 200 per quality-adjusted life-year for strategies 2 and 3, respectively. Monte Carlo simulation found that the chance of incremental cost-effectiveness was 55% for strategy 2 and 71% for strategy 3 (willingness to pay \leq \$50 000 per quality-adjusted life-year). Both strategies 2 and 3 would avert 13 SCDs per 400 000 children seeking stimulant treatment for ADHD, for a cost of \$1.6 million per life for strategy 2 and \$1.2 million per life for strategy 3.

Conclusions—Relative to current practice, adding ECG screening to history and physical examination pretreatment screening for children with attention deficit/hyperactivity disorder has borderline cost-effectiveness for preventing SCD. Relative cost-effectiveness may be improved by basing cardiology referral on ECG alone. Benefits of ECG screening arise primarily by restricting children identified with SCD risk from competitive sports. (*Circulation*. 2010;121:1329-1337.)

Key Words: death, sudden ■ drugs ■ electrocardiography

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental condition, affecting \approx 5% of the general population under 19 years of age.¹ Stimulant medications (eg, methylphenidate and amphetamine preparations) are considered standard treatment of ADHD.^{2,3} It is estimated that 2 to 3 million children are medicated annually in the United States.^{4,5} Stimulants have adrenergic effects and cause modest but statistically significant increases in heart rate and blood pressure.⁶

Editorial see p 1283 Clinical Perspective on p 1337

Sudden cardiac death (SCD) in youth has an estimated annual incidence between 0.8 and 6.2 per 100 000 persons <21 years of age.⁷ Cardiac abnormalities have been found postmortem in up to two thirds of SCD cases.⁷ Concerns about a possible increased risk for SCD during therapeutic use of stimulants in children have been raised after anecdotal

reports were made to the Adverse Events Reporting System of the Food and Drug Administration.⁸ In 2006, the Food and Drug Administration added a warning label to stimulants indicating that they were generally contraindicated for children with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may increase their vulnerability to the sympathomimetic effects of these medications.⁹ Adding to these concerns, a recently reported case-control study found a higher rate of stimulant use among children who died of SCD (1.8%) than among peers who died in car accidents (0.4%).¹⁰

Most clinical guidelines currently recommend pretreatment screening via careful history and physical examination (H&P), with cardiology referral and ECG only in cases of abnormal cardiac examination, personal history of cardiac symptoms, or family history of SCD.^{2,3,11} A recent American Heart Association scientific statement reports that ECG screening corresponds to an evidence-based class IIa recom-

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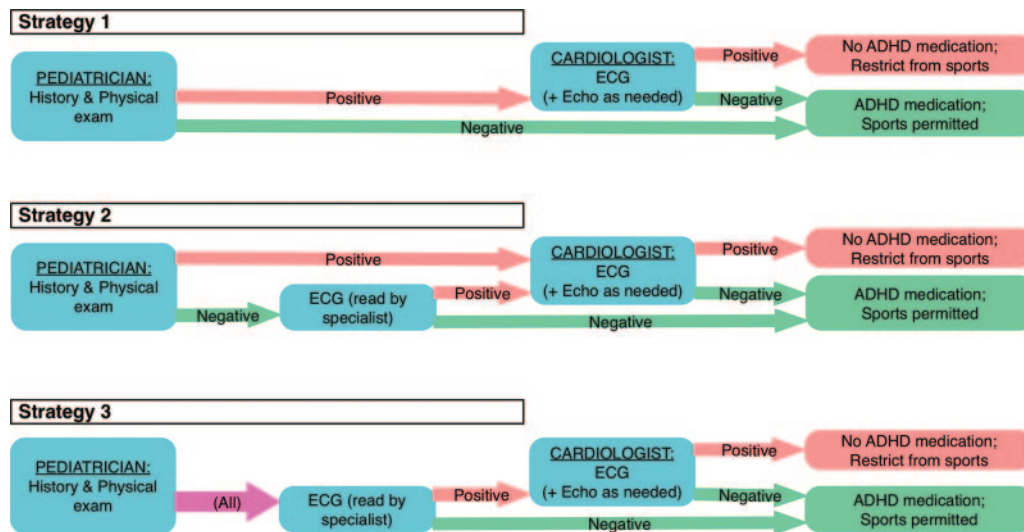


Figure 1. Alternative strategies to screen for cardiac abnormalities in children with ADHD. Strategy 1 reflects current practice. Strategies 2 and 3 reflect alternative clinical decision rules for ECG and cardiology referral.

mentation; ie, it is reasonable but not mandatory to obtain an ECG for children with ADHD being evaluated for stimulant treatment.¹² This statement resulted in public concerns about associated costs and an absence of evidence of potential incremental benefits.¹³ Recent evidence indicates that an increasing number of clinicians are including an ECG in the assessment of children before prescribing stimulants.¹⁴

A similar debate has taken place about screening adolescents entering competitive athletics.¹⁵ Strenuous exercise is a well-documented risk factor for arrhythmias leading to sudden death,¹⁶ and this risk is greater in individuals with cardiac abnormalities such as hypertrophic cardiomyopathy, anomalous coronary artery, myocarditis, arrhythmogenic right ventricular dysplasia, or primary electric abnormalities like long-QT syndrome.¹⁷

We conducted a cost-effectiveness analysis of 2 approaches for routine ECG screening in addition to H&P for children with ADHD to identify those at potential increased risk of SCD before prescribing stimulant treatment compared with the current standard strategy of cardiology assessment only in cases of potential cardiac abnormalities identified through H&P.

Methods

A state-transition Markov model¹⁸ was constructed to evaluate the cost-effectiveness of 3 strategies to screen 7-year-old children with ADHD for heart disease (HD) known to increase risk for SCD. The end points for the analysis were costs of screening and ADHD treatment, quality-adjusted life-years (QALYs), and premature deaths averted.

HD Screening Strategies

We compared 3 main screening strategies to identify SCD risk, shown in Figure 1. Strategy 1 was H&P, with children with potential abnormalities referred for pediatric cardiology evaluation. Strategy 1, the current standard of care, was used as a reference to estimate the cost-effectiveness of 2 alternative strategies: strategy 2, H&P plus ECG in children with negative H&P, with children with abnormalities on either test referred for definitive cardiology evaluation; and strategy 3, H&P plus ECG, with referral for cardiology evaluation only if the ECG is abnormal. Under each strategy, patients can be

divided into 4 subgroups: those without HD who also screen negative (true negatives), those with HD who are missed by the screening (false negatives) who are treated like true negatives, those with HD who are correctly identified and thus restricted from certain activities (true positives), and those without HD who incorrectly screen positive (false positives) whose treatment and activities are restricted unnecessarily.

ADHD Treatment

We assumed that children without an identified HD (ie, true and false negatives) would initiate stimulant treatment for ADHD and be eligible to play competitive sports, whereas those with an identified HD (ie, true and false positives) would be restricted from stimulants and competitive sports. Among children who initiate stimulants, we assumed that some would discontinue quickly because of a lack of response.¹⁹ Of children who respond to medication, some would experience persistent adverse effects such as insomnia, and the remainder would have benefits without adverse effects.²⁰ The model accounts for the natural process of remission of ADHD from 7 to 25 years of age^{21,22} and for medication discontinuation for other reasons.²³

Markov Transition Model

We model HD screening at 7 years of age and ADHD treatment from 7 to 17 years of age divided into 10 annual Markov cycles. Figure 2 shows the complete set of Markov states and transitions between them. Transitions relate to having and remitting from ADHD, stimulant treatment with and without side effects, and mortality, which is affected by HD and associated factors, particularly stimulant treatment and participation in sports.

Table 1 presents our assumptions about the values of model parameters and of transition probabilities between Markov states.^{3,24–36} Parameter values were based on published research or on expert opinion within the research team when no relevant research was available. The model specifically incorporates uncertainty in parameter values. In particular, Table 1 lists ranges for most parameters, which were assumed to follow a β distribution; in addition, we systematically varied the values of key parameters in sensitivity analyses, as discussed further below.

We assume that stimulants for ADHD increase the risk of SCD in children with HD. Because neither the size nor even the existence of such an effect has been proven, we used a conservative base-case value of 10% (ie, 10% over the baseline SCD rate), which we varied extensively in sensitivity analysis. Because SCD is obviously not the only cause of death, we also accounted for death resulting from other causes from 7 to 17 years of age, as well as “residual” longevity after

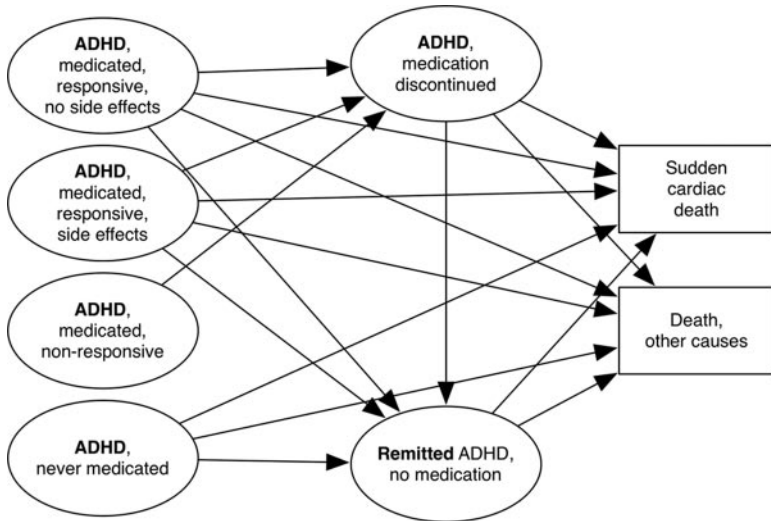


Figure 2. ADHD transitions over time. The circles illustrate alternative states for ADHD and ADHD treatment. The arrows indicate the possible transitions from state to state between the cycles associated with transition probabilities in Table 1.

17 years of age, using the gender-specific 2004 US life table,²⁷ assuming an initial 2:1 male-to-female ratio for ADHD.³⁵

We assessed the costs of the medication, associated medication management visits, and the value of patient/parent time associated with treatment. We assumed that ECGs ordered by pediatricians would be read by someone with appropriate training and require a separate medical appointment from the H&P appointment and that cardiology evaluation would involve ECG in all cases and echocardiogram in 85% of cases. Unit costs were assigned using the 2009 Medicare Physician Fee Schedule for physician services, ECG, and echocardiogram, as well as the 2008 Red Book for stimulants.^{24,25}

Health state utilities for ADHD are scarce in the literature. We used utilities assessed from parents of ADHD children using standard gamble methods.²⁰ Values and associated ranges are listed in Table 1. Because the 95% confidence intervals around the published values for different utility states overlap, we required that the utility of successful medication without side effects be higher than medication with side effects, which in turn was higher than the utility of untreated ADHD.

In addition to the assumptions described in Table 1, we made several assumptions that affected the structure of the decision model:

1. The prevalence of HD with associated SCD risk, the risk of SCD in children with HD, and all-cause mortality are independent of having ADHD.
2. Among people without HD, mortality is independent of sports participation and ADHD stimulant treatment.
3. In the absence of intervention, participation in competitive athletics is independent of having ADHD.
4. The effective sensitivity and specificity of H&P and ECG are independent.
5. The annual ADHD remission rate is constant from 7 to 25 years of age; remission is a binary and absorbing state; and people discontinue stimulants on remission.
6. The annual rate of discontinuation of stimulants is constant from 7 to 17 years of age, and it is independent of side effects among responders.
7. All children identified with HD comply with recommendations to avoid stimulant treatment and competitive athletics.
8. Children with no response to stimulants within 2 months discontinue the medication.
9. Children who respond to stimulants remain responsive through 17 years of age (although they may discontinue earlier for other reasons).

Additional information about the assumptions underlying Table 1 and our decision model is available by request from the authors.

Analysis

We conducted analyses from the societal perspective. Costs and QALYs were discounted at 3% in the base case.^{30,36} Societal willingness to pay was assumed to be ≤\$50 000/QALY. Expected-value analysis and Monte Carlo simulation were performed. Costs and quality-adjusted life expectancies were calculated for each strategy and used to estimate incremental cost-effectiveness (ICE) relative to strategy 1. Monte Carlo simulation used 1000 trials, each with 400 000 patients, to assess the precision of cost-effectiveness estimates. In each trial, model parameters were randomly sampled across their respective β distributions.

One-way expected value sensitivity analyses were performed on all individual variables, including the discount rate for the range from 0% to 5%. Two-way analysis was performed for SCD risk from playing competitive sports versus percentage of students playing such sports because both strongly affect the model but are poorly documented. Analyses used TreeAge Pro Healthcare 2009 software (TreeAge, Williamstown, Mass).

Results

Base-Case Analysis

Table 2 presents the expected cost and effectiveness of strategies 1 through 3 and the expected ICE of strategies 2 and 3 relative to strategy 1. Relative to strategy 1, strategy 2 raises costs by \$52 and adds 0.0013 QALYs per capita, corresponding to an ICE of \$39 300/QALY; strategy 3 raises costs by \$38 and adds 0.0014 QALYs per capita for an ICE of \$27 200/QALY. Notably, strategy 3 formally dominates strategy 2, having both lower costs and better outcomes.

Monte Carlo Simulation

Figure 3 shows the incremental costs and effectiveness of strategies 2 and 3 relative to strategy 1. The diagonal line represents the target societal cost threshold of \$50 000/QALY, with trials to the right of that line signifying lower (ie, more favorable) ICE. On the basis of that threshold, strategy 2 has a 55% probability of cost-effectiveness relative to strategy 1, whereas strategy 3 has a 71% probability of cost-effectiveness. The relatively wide scatter for strategy 2 is due to the application of 2 screening procedures (H&P plus ECG), each involving some uncertainty.

Table 3 shows the estimated number of SCDs per 400 000 patients between 7 and 17 years of age. Both strategies 2 and

Table 1. Model Input Variables

Parameter	Base Case	Range	Source
Unit costs, \$			
Initial patient visit (H&P examination) (CPT 99203)	92	67–117	Reference 24
Cardiologist visit (CPT 99244)	185	150–220	Reference 24
ECG (CPT 93000)	23	20–44	Reference 24
Echocardiogram (CPT 93303+93320+93325)	350	280–420	Reference 24
ADHD medication (per day)	4.25	3.25–5.25	Reference 25*
Medication management visit (CPT 99241)	50	45–85	Reference 24
Patient/parent time (per visit)	20	17–41	Estimate
Treatment volume, initial year			
Fraction of cardiology visits that include echocardiogram	0.85	N/A	Estimate
Days of ADHD medication (if medicated)	365	N/A	Reference 3
Medication management visits	4	N/A	References 3, 26
Treatment volume, maintenance phase (per year)			
Days of ADHD medication (if medicated)	365	N/A	Reference 3
Medication management visits	4	N/A	Reference 3
Event probabilities, ADHD treatment and remission			
Of positive response to ADHD medication	0.87	N/A	Reference 19
Of medication side effects if positive response	0.053	N/A	Reference 20
Of discontinuing ADHD medication if nonresponse	1.00	N/A	Assumption 7
Of discontinuing ADHD medication if responsive (per year)	0.10	N/A	Reference 23
Of ADHD remission (per year, up to 25 y of age)	0.02365	N/A	Reference 21, 22
Of discontinuing ADHD treatment if remission	1.00	N/A	Assumption 4

(Continued)

Table 1. Continued

Parameter	Base Case	Range	Source
Event probabilities, SCD and associated with it factors			
Prevalence of HD with risk of SCD	0.001	0.0005–0.0045	Reference 17
Of death if no HD with SCD risk (by age and sex)	US life table	N/A	Reference 27
Of SCD if HD with SCD risk, not identified (per year)	0.015	0–0.03	Reference 28
Of SCD if HD with SCD risk, identified (per year)	0.00974	0–0.0195	Calculated
Additional risk of SCD if HD with SCD risk+ADHD medication (multiplier)	1.10	1.0–1.8	Estimate
Additional risk of SCD if HD with SCD risk+playing competitive sports (multiplier)	2.80	1.8–3.8	Reference 16
Of playing competitive sports	0.30	0.10–0.50	Estimate
Sensitivity and specificity for detecting HD with risk of SCD			
Sensitivity (H&P)	0.04	0.01–0.07	Reference 29
Specificity (H&P)	0.955	0.85–1.00	Reference 30
Sensitivity (ECG)	0.70	0.65–0.75	References 31, 32
Specificity (ECG)	0.955	0.85–1.00	References 31–33
Sensitivity (ECG+H&P; strategy 2)	0.71	0.65–0.77	†
Specificity (ECG+H&P; strategy 2)	0.91	0.72–1.00	‡
Sensitivity of the cardiologist (ECG+echocardiogram as needed)	0.90	0.80–1.00	§
Specificity of the cardiologist (ECG+echocardiogram as needed)	0.98	N/A	§
Quality of life (1=perfect health, 0=death)			
ADHD, no treatment	0.88	0.826–0.934	Reference 20
ADHD, treated with and responsive to medication, no side effects	0.93	0.907–0.953	Reference 20
ADHD, treated with and responsive to medication, side effects	0.912	0.885–0.939	Reference 20
Remitted ADHD	0.95	0.93–0.97	Estimate
ADHD, age ≥17 y	0.91	0.89–0.93	Estimate

(Continued)

Table 1. Continued

Parameter	Base Case	Range	Source
Total discounted QALYs if survival to 17 y of age, ADHD remitted by 17 y of age			
No SCD risk	19.726	N/A	Calculated
SCD risk, identified	16.130	N/A	Calculated
SCD risk, unidentified	14.611	N/A	Calculated
Total discounted QALYs if survival to 17 y of age, ADHD not remitted by 17 y of age			
No SCD risk	19.161	N/A	Calculated
SCD risk, identified	15.666	N/A	Calculated
SCD risk, unidentified	14.190	N/A	Calculated
Other			
Initial age, y	7	N/A	Reference 34
Initial fraction of cohort that is male	0.667	N/A	Reference 35
Years covered by model (=n Markov cycles)	10	N/A	
Discount rate	0.03	N/A	References 30, 36

*Based on simple average of cost per day for 20 mg Adderall XR, 36 mg Concerta, 20 mg Focalin XR, 40 mg Methylin ER, 40 mg Ritalin LA, and 40 mg of Ritalin SR.

†Assuming that the 2 tests are independent: $sensitivity_{H\&P+ECG} = sensitivity_{H\&P} + sensitivity_{ECG} - sensitivity_{H\&P} \times sensitivity_{ECG}$.

‡Assuming that the 2 tests are independent: $specificity_{H\&P+ECG} = specificity_{H\&P} \times specificity_{ECG}$.

§Estimate based on combination of sensitivity and specificity for echo³⁵ and ECG, respectively.

3 avert ≈13 SCDs per 400 000 people relative to strategy 1, but strategy 3 is less costly. Thus, the estimated cost per incremental SCD averted is \$1.6 million with strategy 2 and \$1.2 million with strategy 3. Table 3 also illustrates the number of pediatric cardiology visits under each strategy overall and for true-positive cases.

Sensitivity Analysis

Figure 4 shows the effect of varying critical input parameters on the ICE of strategies 2 and 3 relative to strategy 1. Figure 4 shows that estimated incremental cost per QALY increases exponentially with declines in prevalence of HD with SCD risk and the decline in the annual SCD rate. For strategies 2 and 3 to be cost-effective at the target societal threshold of

\$50 000/QALY, the prevalence of HD with SCD risk would need to be at least 85% and 60%, respectively, of the base-case value of 0.1% (Figure 4A). The annual rate of SCD in HD patients would need to be 0.0115 and 0.0065 to preserve the cost-effectiveness of strategies 2 and 3, respectively, compared with the base-case value of 0.015 (Figure 4B).

The low incidence of SCD makes the model sensitive to the specificity of ECG: ECG specificity should be >93% and 89% for strategies 2 and 3, respectively, to maintain cost-effectiveness relative to current practice compared with the base case of 95.5% (Figure 4C). In contrast, the ICE of strategy 2 is virtually insensitive to H&P specificity (Figure 4D), whereas the ICE for strategy 3 improves with the decline of the H&P specificity because H&P affects costs and outcomes in strategy 1 but only costs in strategy 3. Indeed, if the specificity of H&P falls below 84%, strategy 3 becomes cost-saving relative to strategy 1 because the total cost of pediatric cardiologist visits resulting from false positives from H&P under strategy 1 exceeds the costs of ECGs under strategy 3.

Finally, the ICE of strategies 2 and 3 is substantially more sensitive to sports participation rate (Figure 4F) than from stimulant treatment (Figure 4E). In particular, even if the incremental risk of stimulants for at-risk children were zero, strategies 2 and 3 would remain relatively cost-effective. This is not the case with the sports participation rate; the critical values above which the strategies remain cost effective are 23% (strategy 2) and 13% (strategy 3) compared with the base case of 30%.

The 2-way sensitivity analysis in Figure 5 shows that reductions in the base rate of participation in competitive athletics and in the associated risk of SCD significantly increase the incremental cost per QALY for strategy 2. Strategy 3 is less sensitive to these parameters. Information on additional sensitivity analyses is available by request.

Discussion

The cost-effectiveness of 3 different strategies to screen children with ADHD for HD with SCD risk before stimulant treatment was evaluated. The main finding is that the cost-effectiveness of adding 12-lead ECG screening to standard H&P pretreatment evaluation can be considered borderline at \$39 300/QALY; the cost per SCD averted is \$1.6 million. In comparison, strategy 3 has a more favorable ICE, with an incremental cost per QALY of \$27 200 and cost per averted SCD death of \$1.2 million relative to current practice.

The finding that 2 screens (H&P and ECG) are less cost-effective than 1 (ECG) is determined by 2 factors. First, the net sensitivity of strategy 2 (0.71) is virtually the same as for

Table 2. Expected Costs, Effectiveness, and ICE Relative to Strategy 1

Strategy	Cost, \$		QALY		ICE, \$/QALY
	Total (per Person)	Incremental (per Person)	Total (per Person)	Incremental (per Person)	
Strategy 1	9972		27.263 413
Strategy 2	10 024	52	27.264 682	0.001 269	39 300
Strategy 3	10 010	38	27.264 800	0.001 387	27 200

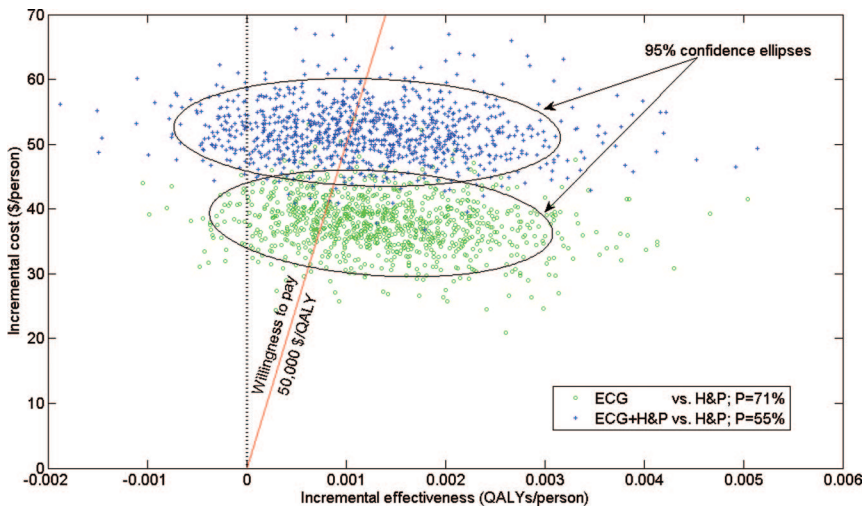


Figure 3. Incremental cost and effectiveness of strategies 2 and 3 relative to strategy 1. The scatterplot shows the results of 1000 Monte Carlo simulation trials for strategies 2 (pluses) and 3 (circles). The 2 ellipses correspond to the 95% confidence intervals around the 2 respective sets of results. The diagonal line represents the target societal cost threshold of \$50 000/QALY, with trials to the right of that line signifying lower (ie, more favorable) ICE.

strategy 3 (0.70), so the number of “true-positive” cases is nearly identical under both strategies. Second, however, strategy 2 would refer 16 000 additional “false-positive” cases for cardiology assessment relative to strategy 3. As long as cardiologist assessment is not perfectly specific, strategy 2 will deprive more children without HD of the benefits of stimulant treatment for ADHD compared with strategy 3 (7200 versus 4000, respectively, at the base specificity of 0.98).

Notably, the ICE values of strategies 2 and 3 seem to be largely insensitive to incremental SCD risk from stimulants. In particular, even when this risk is zero, both strategies remain cost-effective relative to current practice. The major benefit of screening appears to be the opportunity to identify children with HD and restrict them from competitive sports. It follows that our principal findings are likely to apply to HD screening in children overall independently of ADHD, particularly in candidates for competitive sports; we will examine this topic in future research.

The debate over ECG screening continues because of inadequate evidence.^{37,38} Using simplified methodology, Fuller³² demonstrated that ECG screening was more cost-effective than H&P for high school athletes. Alternatively, Maron et al¹⁷ estimated that a mass preparticipation screening program that included ECG would cost \$2 billion annually in the United States. Obtaining definitive data is hampered by the low incidence of cardiac events and the large population and high costs that a definitive clinical trial would require. The rigorous decision model and cost-effectiveness analysis presented here are intended to inform the current debate. The model synthesizes data from all available sources, incorpo-

rates uncertainty, and projects to hard end points (notably mortality). Within this context, the model compares the effectiveness and costs of the competing strategies but also projects resource and personnel requirements.

Specific findings from this model may inform the debate over the use of ECGs as a screening tool. First, our study demonstrates that cardiology referral based on ECG alone, ignoring potentially conflicting H&P findings, dominates a strategy that refers on the basis of either assessment. The clinical applicability of such a strategy is uncertain, but it suggests that novel screening strategies may be more cost-effective than those typically recommended. Second, the finding that the potency of screening is related to the ability to restrict at-risk patients from competitive sports has implications for the general pediatric population, regardless of possible exposure to stimulant treatment. Finally, the model identified several variables for which the model was very sensitive. These included prevalence of HD with SCD risk, the annual risk of SCD in at-risk patients, the specificity of ECG, and the base rate of participation in sports and the associated SCD risk. Better evidence relative to these parameters would likely improve the precision of decision analysis and help target future intervention trials.

This study should be interpreted in light of several important limitations. Perhaps most important, as already noted, there was limited existing evidence on important model parameters. When data were available, they were derived primarily from cohort and observational studies, which are more susceptible to bias than randomized trials; in other cases, however, such as our assumption that the specificities of ECG and H&P were independent, we are not aware of any corresponding literature.

In the absence of definitive evidence, we were able in some cases to assess the likely effect of bias if an assumption was incorrect. For instance, in the particular example relative to specificity of ECG and H&P, if a positive correlation does exist, the effectiveness of strategy 2 will increase with this correlation; in the extreme case of perfect correlation, the effectiveness of strategies 2 and 3 will be approximately equal. As another example, we assumed that the rate of SCD in children with identified HD is equivalent to the rate of SCD

Table 3. SCDs and Visits to a Pediatric Cardiologist per 400 000 Patients Estimated by Monte Carlo Simulation

Strategy	SCDs		Visits to a Pediatric Cardiologist (True Positives)	
	n	SE	n	SE
1	58	24	18 000 (16)	3000 (7)
2	45	19	35 000 (282)	4000 (74)
3	45	19	18 000 (277)	3000 (73)

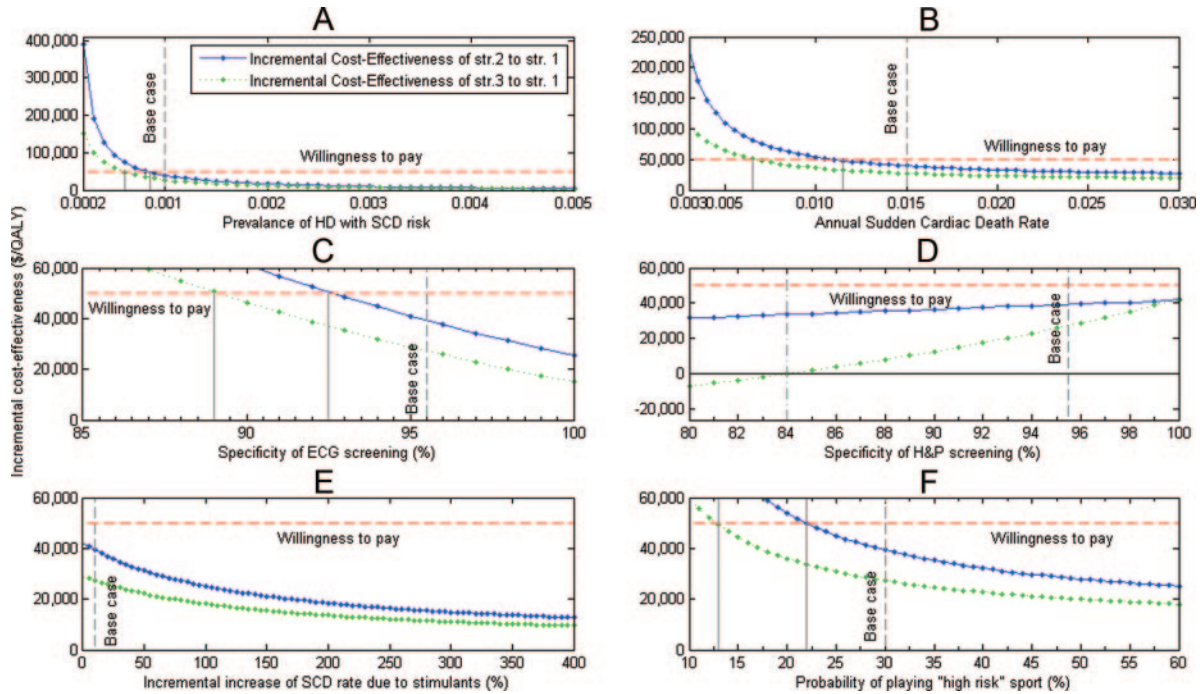


Figure 4. One-way sensitivity analyses of key parameters. In each plot, ICE is represented on the vertical axis and the parameter value on the horizontal axis. Strategies 2 and 3 are presented by blue and green lines, respectively; willingness to pay threshold, by red horizontal dashed lines; and the base-case values of the varied parameters, by vertical gray dashed lines. A, The cost per QALY increases exponentially with decreases in the prevalence of HD with SCD risk; below 85% (strategy 2) or 60% (strategy 3) of the base value, ICE exceeds the target cost threshold of \$50 000/QALY. B, ICE exceeds the target when the annual SCD rate falls below 75% (strategy 2) or 45% (strategy 3) of the base value. C, ICE increases approximately linearly with changes in the specificity of ECG screening; ICE exceeds the target if ECG specificity falls below 92.5% (strategy 2) or 89% (strategy 3). D, The ICE of strategy 2 relative to strategy 1 is insensitive to the specificity of H&P, whereas if H&P specificity drops under 84%, strategy 3 will dominate strategy 1. E, Strategies 2 and 3 remain relatively cost-effective even if stimulants pose zero SCD risk. F, ICE exceeds the target if participation in competitive sports falls below 22% (strategy 2) or 13% (strategy 3).

in children with unidentified HD who do not play sports or take stimulants. The model does not take into account potential therapies that can be instituted for children with identified HD that may further lower their risk of SCD (ie, β -blockers, implantable cardioverter-defibrillators). Although the effects of

such therapies on the model depend on their cost and effectiveness, it is likely that they would further improve the ICE of strategies 2 and 3 relative to current practice.

A similar conservative bias is induced for strategy 3 by the fact that we count the cost of H&P as part of that strategy,

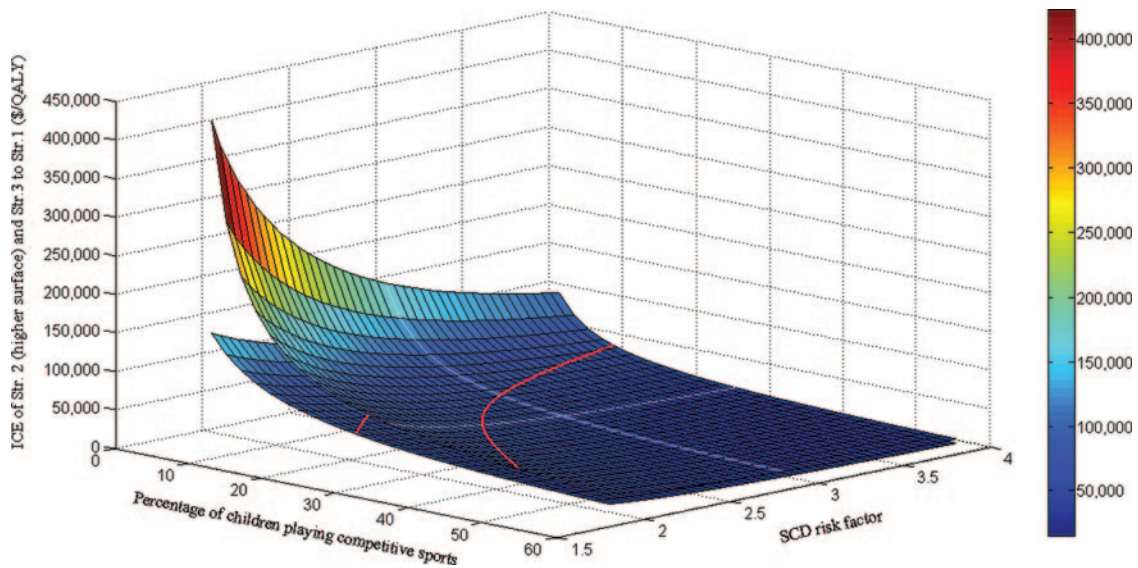


Figure 5. Two-way sensitivity analysis of participation in competitive sports vs sports-related incremental SCD risk. The top and bottom surfaces compare strategies 2 and 3, respectively, with strategy 1. ICE is represented on the vertical axis and by color code. The red curved line represents the target societal cost threshold. Gray lines represent base-case values.

even though clinical decisions are informed only by ECG results. Given that we count the full cost of H&P in strategy 2, despite the fact that H&P may serve purposes beyond identifying SCD risk, it seemed inappropriate to omit these costs entirely from strategy 3. A narrower definition of strategy 3 would reinforce its cost-effectiveness relative to strategies 1 and 2.

Finally, we recognize that stimulant medication is not the only evidence-based treatment for ADHD. We have extended the decision model presented here to include scenarios in which children with ADHD who are identified with HD or are nonresponsive to stimulants receive a psychotherapeutic behavioral management intervention.³⁹ In qualitative terms, this did not alter our main substantive findings. Details are available by request from the authors.

Conclusions

These models, together with the detailed sensitivity analyses and simulations, suggest that adding ECG screening to current practice has borderline cost-effectiveness for identifying children at risk of SCD before initiating stimulant medication for ADHD. Cost-effectiveness can be improved by eliminating the accompanying H&P from the screening program. As is often the case in medical care, there is substantial uncertainty surrounding several of the underlying assumptions, which likely reflects a wide variability in clinical situations and precision of assessments. When this uncertainty is taken into account, adding ECG to H&P has a 55% probability of being cost-effective at or below the target of \$50 000/QALY relative to current practice.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Stimulants are commonly used to treat children with attention deficit/hyperactivity disorder. These drugs have adrenergic properties and may increase the risk for sudden cardiac death in individuals with cardiac abnormalities such as cardiomyopathies or conduction defects. Although the possible value of routine ECG screening before stimulant treatment is an object of debate, current clinical guidelines recommend medical history taking and physical examination, with ECG and cardiology evaluation only for the children who screen positive on history taking and physical examination. In the first such study, we conducted a modeled economic evaluation of 3 different approaches to screening children for possible cardiac abnormalities before stimulant treatment. The analyses indicate that adding ECG to history taking and physical examination would prevent sudden cardiac death at an estimated cost of about \$39 000 per quality-adjusted life-year. Because of the low sensitivity and specificity of history taking and physical examination, relying exclusively on an ECG screening would lead to the more favorable cost of about \$27 000 per quality-adjusted life-year. Monte Carlo simulations suggest that screening with ECG has borderline cost-effectiveness according to generally accepted willingness-to-pay criteria. These analyses provide useful estimates that contribute to the current debate on the possible role of ECG for preventing sudden cardiac death in childhood.