

Hormonal Contraceptive Use and Risk of Depression Among Young Women With Attention-Deficit/Hyperactivity Disorder

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Objective: Women with attention-deficit/hyperactivity disorder (ADHD) have an increased risk of becoming teenage mothers. Adverse effects of hormonal contraception (HC), including depression, may affect adherence to user-dependent contraception and increase the risk for unplanned pregnancies and teenage births in women with ADHD. The current study analyzed whether girls and young women with ADHD are at increased risk for depression during HC use compared with women without ADHD.

Method: A linkage of Swedish national registers covering 29,767 girls and young women with ADHD aged 15 to 24 years and 763,146 without ADHD provided measures of ADHD and depression diagnoses (*International Classification of Diseases [ICD]* code) and prescription of stimulant medication, HC, and antidepressant medication (Anatomical Therapeutic Chemical [ATC] code). Cox regression models applying an interaction term (ADHD diagnosis \times HC use) evaluated the excess risk of HC-induced depression in women with ADHD.

Results: Women with ADHD had a 3-fold higher risk of developing depression, irrespective of HC use (adjusted hazard ratio [aHR] = 3.69, 95% CI = 3.60-3.78). Oral combined HC users with ADHD had a 5 times higher risk of depression compared with women without ADHD who were not using oral combined HC (aHR = 5.19, 95% CI = 4.94-5.47), and a 6 times higher risk in comparison with women without ADHD who were on oral combined HC (aHR = 6.10 (95% CI = 5.79-6.43). The corresponding risk of depression in women with ADHD who used a progestogen-only pill (aHR = 5.00, 95% CI = 4.56-5.49). The risk of developing depression when using non-oral HC was similarly moderately increased in both groups.

Conclusion: Girls and young women with ADHD have an increased risk of developing depression when using oral HC compared with their unaffected peers. Information on risks with HCs as well as potential benefits with long-acting reversible contraceptives needs to be an integrated part of the shared decision making and contraception counseling for young women with ADHD.

Key words: ADHD; women; hormonal contraceptive; depression

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Mental illness is more prevalent in women compared to men.¹ Young women, aged 18 to 25 years, have the highest risk for common psychiatric conditions in comparison with women and men of all age groups,² which in turn may have consequences for their reproductive health. Indeed, research suggests a vicious spiral whereby women with mental health problems are less likely to use effective contraceptive methods.³ Unintended pregnancies at an early age overlap with formative academic and occupational years, and may further enhance negative psychiatric and psychosocial outcomes.^{4,5}

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent (ie, 3%-7% among adolescents and adults worldwide) and persisting (ie, about 50%-75% continuation in adulthood) neurodevelopmental disorder^{6,7}

associated with severe adverse psychosocial and somatic outcomes across the lifespan and a substantial economic burden on society.⁸⁻¹⁰ More specifically, women with ADHD are at high risk for mental health impairment,¹¹ admissions to inpatient psychiatric care,¹² risky sexual behavior, exploitation, and victimization.¹³ Of importance for this study, women with ADHD are, despite widespread availability of hormonal contraception and low overall rates of teenage pregnancies in Sweden,¹⁴ 6 times more likely to give birth as teenagers compared with women without this diagnosis.¹⁵

It is yet not known why women with ADHD are more prone to becoming teenage mothers. Several pathways are possible, including failure to access available contraceptives, substandard contraceptive counseling, lack of adherence, or

failure to find a contraceptive that they tolerate. This study addresses the last of these possibilities, namely, whether women with ADHD are more prone to developing depression during hormonal contraceptive (HC) use than are women without ADHD.

Overall, the association between HCs and the risk for depression is debated, and consensus is lacking. Some large register-based studies have shown increased risk of depression, use of antidepressant, anxiolytic, hypnotic, or sedative medication following HC use, particularly for young women,^{16,17} whereas other studies report that the most common preparations, namely the combined hormonal contraceptive (COC) or progestogen-only pill (POP), are not associated with any risk for depression.¹⁸ Randomized controlled trials (RCTs) of COC or placebo demonstrate minor mood dysregulation upon active treatment.¹⁹⁻²¹ The latter finding was driven primarily by women with a history of mental health problems,²² suggesting that there may be certain subgroups of women more vulnerable to COC-related side effects and mental symptoms. Although a causal link between HC use and depression is still debated, experiencing mental side effects is indeed the most commonly reported reason for discontinued HC use in the general population.²³ Moreover, women who discontinue HC because of mental side effects, whether it is minor depressive symptoms or a treatment-requiring depressive episode, do so in spite of continued need for contraception.²⁴ They may turn to less effective contraceptive methods and become at increased risk for unintended conception and induced abortion.^{25,26}

The adverse psychosocial outcomes associated with ADHD in girls and young women may influence the trajectory toward adolescent and adult psychopathology, including depression and anxiety.²⁷ Thus, adverse psychosocial experiences may add to an already increased risk for psychiatric comorbidity transferred through common genetic risk factors.²⁸ To mitigate further adverse psychosocial outcomes, such as teenage pregnancies, it is essential to explore why contraceptive counseling may fail women with ADHD. Drawing on the finding of increased risk of teenage pregnancies in women with ADHD and on contraceptive RCTs demonstrating that women with mental health problems are more prone to experiencing mental side effects from HC, the aim of this study was to determine whether women with ADHD are more susceptible to developing depression from HCs than are women without the diagnosis. Expanded knowledge on safe and feasible contraception for women with ADHD will provide clinicians with guidance in contraception counseling.

METHOD

Data sources

This cohort study was based on data from Swedish national population-based registers. The National Board of Health and Welfare provided data from the Swedish Prescribed Drug Register (PDR), the National Patient Register (NPR), and the Cause of Death Register (CDR). Statistics Sweden provided data from the Total Population Register (TPR), the Multi-Generation Register (MGR) and the Education Register.

The PDR enables drug identification through Anatomical Therapeutic Chemical (ATC) classification codes and provides data on dispensed prescriptions for the entire Swedish population since July 1, 2005, including prescriptions issued from primary health care.²⁹ The NPR was established in 1964 and contains information on dates of inpatient care and corresponding somatic and psychiatric diagnoses classified according to the *International Classification of Diseases and Related Health Problems (ICD)*, with complete national coverage since 1987.³⁰ Since 2001, the NPR has also recorded specialist outpatient visits. Data from primary health care visits including nonspecialist physicians and midwives are not covered within the register.³⁰

The CDR provides dates and causes of all registered deaths since 1952.³¹

The TPR covers information on the identity of all Swedish residents, registered as living in Sweden at some point since 1961. The MGR emanates from the TPR and provides information on any relationship to (biological or adoptive parents) individuals born since 1932.³² The Education Register contains information on the highest level of educational attainment in all Swedish individuals. The personal identity number allocated to all people living in Sweden (by birth or immigration) allows linkage of data across registries.³³

Each somatic or psychiatric diagnosis referred to in the study was classified according to the *ICD* revised according to the year of the initial registered diagnosis.³⁴

Study Population

All Swedish-born women aged 15 to 24 years at any time between January 1, 2010, and December 31, 2017, and residing in Sweden were identified through the TPR and included in the study.

Women with a medical condition that constitute a contraindication against use of HCs, for example, malignancies in breast or genital organs (*ICD-10* codes D05, C50-C58), any cardiovascular disease including deep vein

thrombosis (*ICD-10* codes I10-I50, I20-I25, I26-I28, I42-I46, I49, I63, I74, I81-I82, O00-O007, O22, O87), infertility including redeemed prescription of ovulation-stimulating drugs (*ICD-10* code N97, ATC code G03G), systemic lupus erythematosus (*ICD-10* code M32), and migraine with aura (*ICD-10* code G43.1) 5 years before entering the study were excluded.

Similarly, to capture incident cases of depression, we excluded women with a diagnosis of mental or behavioral disorders (*ICD-10* code F05-F89, F91-F99), or antidepressant treatment (ATC classification N06A) 5 years before the study start (4.5 years for women who entered the study in 2010).

Exposure

This study had 2 exposures: ADHD diagnosis and HC use. Women with ADHD were identified by a diagnosis of any hyperactivity disorder (*ICD-10* code F90) and/or a prescription of any ADHD medication (ATC classification code N06BA). We identified 26,406 women with an in- or outpatient diagnosis of hyperkinetic disorder (HKD) (F90 in *ICD-10*) between January 1997 and December 2017 from the NPR. Furthermore, we identified 21,941 women who had filled at least 2 prescriptions of stimulant or nonstimulant medication for ADHD (methylphenidate [N06BA04], atomoxetine [N06BA09], amphetamine [N06BA01], dexamphetamine [N06BA02]) at any time between July 2005 and December 2017 via the PDR. Altogether, 29,767 unique ADHD cases were identified after adjustment of overlaps between the 2 registers. Swedish national guidelines state that stimulant medications are restricted for ADHD treatment and should only be used for ADHD together with other supportive interventions.³⁵ We considered ADHD as a chronic condition with symptoms before age 12 years.³⁶ By this, women were classified as having ADHD if they fulfilled either of the above criteria at any time-point during the study period, that is, they were considered as ADHD women also before they were diagnosed. All remaining women in the cohort were classified as women without ADHD.

Women who were treated with any HC between January 1, 2010, and December 31, 2017, were identified through the PDR. HC can only be dispensed in Sweden using a prescription issued by a physician or a midwife; thus, all users during the study period have been included in the study. As with any study-specific outcome due to hormonal exposure, adverse events are unlikely within the first month of treatment; therefore, we considered women to be unexposed the first 28 days following a redeemed HC prescription. Oral HCs and

contraceptive patch/vaginal ring can be prescribed for 3 or 12 months. The duration of use was estimated according to the defined daily dose (DDD) information available for each filled prescription. Similarly, the hormonal intrauterine device (IUD), implant, and injection exposure times were estimated as 5 years, 3 years, and 3 months, respectively (unless women switched to a different HC). All dispensed prescriptions were extended with 28 days to account for persisting effects of HC.

Women contributed with exposed person time and nonexposed person time. We used non-users of HC as a reference group. Non-users included the person time of women who never used HC during the study period, the person time of women prior to their first HC prescription, and person time in former HC users.

HCs were categorized according to route of administration (oral or non-oral) and as combined or progestogen-only products. Seven different HC groups were used; any HC, COC, combined non-oral contraceptives (ie, patch or vaginal ring), progestogen-only pills, progestogen implants, progestogen injection, and the hormonal IUD (Table S1, available online).

Outcomes

Depression among women with or without ADHD was defined as a first depression diagnosis in the NPR (*ICD-10* codes F32-F33.9) between January 1, 2010 and December 31, 2017, and/or a redeemed prescription for antidepressant treatment (ATC code N06A) in the PDR.

Covariates

The highest attained educational level at the end of the study period was categorized as 9 years (primary school), 10-12 years (secondary school), more than 12 years (university), or unknown. Parental origin was categorized as both parents born in the Nordic countries, one parent born in the Nordic countries, both parents born outside of Europe, or other.

Medical indication for HC use included acne (*ICD-10* code L70), dysfunctional uterine bleeding (DUB) (*ICD-10* codes N91-N943, N948-N949), dysmenorrhea (*ICD-10* codes N944-946), endometriosis (*ICD-10* code N80) and polycystic ovary syndrome (*ICD-10* codes E282 and L68). If any one of the parents of the woman had been diagnosed with a mental or behavioral disorder or had committed suicide (*ICD-8* codes 290-309, E9509-9599, *ICD-9* codes 290-316, E950-E959, *ICD-10* codes F05-99, X60-84), we considered this as a parental history of mental disorders. We retrieved information on the parents from specialized inpatient care between 1971 and 2016 or specialized outpatient care

TABLE 2 Risk of Developing Depression in the Study Population, in Relation to Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis (*n* = 29,767), Any Hormonal Contraceptive Use, and Other Covariates

Covariate	Events/person-years	aHR (95% CI)
ADHD	12,215/95,253	3.69 (3.60-3.78)
Education		
9 y	20,109/431,654	2.16 (2.11-2.21)
10-12 y	43,064/1,500,074	1.34 (1.32-1.37)
University	25,451/1,260,693	1 (ref)
Unknown	2,229/85,544	1.39 (1.33-1.45)
Family		
Both parents from Nordic countries	79,202/2,771,213	1 (ref)
One parent from Nordic countries	6,960/221,232	0.99 (0.97-1.02)
Both parents from outside EU	2,485/162,460	0.50 (0.48-0.52)
Other	2,206/123,061	0.59 (0.56-0.61)
Parental history of mental disorder		
None	56,491/2,425,833	1 (ref)
Psychiatric diagnosis	33,641/837,107	1.51 (1.49-1.53)
Parental suicide	721/15,026	1.76 (1.64-1.89)
Medical indication for HC		
Acne	5,567/161,792	1.29 (1.25-1.32)
Dysfunctional bleeding	7,048/146,026	1.40 (1.37-1.44)
Dysmenorrhea	6,937/118,250	1.80 (1.75-1.84)
Endometriosis	1,304/18,192	1.66 (1.57-1.76)
Polycystic ovary syndrome	2,162/52,828	1.36 (1.30-1.42)
Age		1.06 (1.06-1.06)
Calendar year		1.06 (1.05-1.06)
Any HC use	33,594/1,225,043	0.99 (0.97-1.00)
Interaction ADHD × any HC		1.39 (1.33-1.45)

Note: All variables in the table are adjusted for each other. aHR = adjusted hazard ratio; EU = European union; HC = hormonal contraceptive; ref = reference.

TABLE 3 Risk of Depression in Relation to Type of Hormonal Contraceptive and in Relation to Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis (*n* = 29,767)

Contraceptive	Women with ADHD	Women without ADHD	Main effect of HC exposure	HC × ADHD interaction	
	Events/person-years	Events/person-years	aHR (95% CI)	<i>p</i>	aHR (95% CI) <i>p</i>
Combined oral contraceptive	1,524/9,832	16,899/773,693	0.85 (0.84-0.87)	<.001	1.60 (1.51-1.69) <.001
Progestogen-only pill	453/2,929	4,595/173,518	1.01 (0.98-1.04)	.32	1.22 (1.10-1.34) <.001
Patch and vaginal ring	168/981	1,811/57,745	1.24 (1.18-1.30)	<.001	1.12 (0.95-1.31) .14
Implant	697/8,027	4,091/125,623	1.23 (1.19-1.27)	<.001	0.99 (0.91-1.07) .91
Injection	16/135	156/9,179	1.21 (1.03-1.42)	.51	0.65 (0.39-1.09) .12
Hormonal IUD	267/2,704	3,001/73,329	1.41 (1.36-1.47)	<.001	0.88 (0.78-1.00) .06

Note: Values are adjusted for age, calendar year, level of education, parental country of origin, parental diagnoses of mental disorder, acne, dysmenorrhea, dysfunctional uterine bleeding, endometriosis, polycystic ovary syndrome, age, and calendar year. aHR = adjusted hazard ratio; COC = combined oral contraceptive; HC = hormonal contraceptive; POP = progestin-only pill.

TABLE 4 Hormonal Contraceptive Use and Risk for Development of Depression in Women With and Without ADHD

Contraceptive	Participant group	Events/person-years, (%)	aHR (95% CI)
Combined oral contraceptive	Women without ADHD without COC	61,739/2,409,020 (2.5)	1
	Women without ADHD with COC	16,899/773,693 (2.2)	0.85 (0.84-0.87)
	Women with ADHD without COC	10,691/85,421 (12.5)	3.83 (3.75-3.91)
	Women with ADHD with COC	1,524/9,832 (15.5)	5.19 (4.94-5.47)
Progestogen-only pill	Women without ADHD without POP	74,043/3,009,195 (2.5)	1
	Women without ADHD with POP	4,595/173,518 (2.6)	1.01 (0.98-1.04)
	Women with ADHD without POP	11,762/92,324 (12.7)	4.07 (3.98-4.15)
	Women with ADHD with POP	453/2,929 (15.4)	5.00 (4.56-5.49)

Note: Values are adjusted for age, calendar year, level of education, parental country of origin, parental diagnoses of mental disorder, acne, dysmenorrhea, dysfunctional uterine bleeding, endometriosis, and polycystic ovary syndrome. ADHD = attention-deficit/hyperactivity disorder; aHR = adjusted hazard ratio; COC = combined oral contraceptive; POP = progestin-only pill.

ADHD defined according to ICD diagnosis or ATC code for ADHD medication yielded similar results, with the exception that women with an ADHD diagnosis also had an increased risk of depression with transdermal or vaginal combined HCs in comparison with healthy nonusers (Table S2 and Table S3), available online. Sensitivity analyses of the outcome, that is, depression, showed that the results were robust to the use of ICD diagnosis or ATC code (Table S4 and Table S5, available online).

DISCUSSION

This population-based cohort study explored the association between HC use and the risk of developing depression in women with ADHD compared to women without ADHD, suggesting that women with ADHD are more susceptible to developing depression during HC use than women without ADHD. Further analyses showed that although use of oral HC had no influence on depression in women without ADHD, these contraceptives added to the already elevated risk of developing depression in women with ADHD. In contrast, women with ADHD who used non-oral HCs, such as the implant or hormonal IUD, had a moderate risk of developing depression, which was no different from that in the women without ADHD. Overall, women with ADHD who used COCs or POPs had more than 5 times increased risk of depression compared to women without ADHD who did not use HCs.

In line with previous research, our results show that women with ADHD are at increased risk for developing depression.^{38,39} Independent of HC use and controlling for several confounders such as education and country of origin,

women with ADHD had a more than 3-fold higher risk of developing depression compared to women without ADHD.

We also demonstrate that women with ADHD had a higher risk of developing depression specifically when using oral HCs, whereas the moderate risk for depression with non-oral products did not differ from that in women without ADHD. This is in line with previous research, suggesting that women with prior depression, anxiety, or socioeconomic disadvantage are more inclined to experience adverse mood effects from COCs.^{22,40,41} Prior findings in women with ADHD are, however, lacking. The biological underpinnings of our findings can only be speculated upon. It is unlikely that exogenous hormone exposure *per se* places women at risk, as serum concentrations of contraceptive hormones (eg, ethinyl estradiol in the ring and pills and etonogestrel in the implant and the pill) are similar between oral and non-oral products.⁴² Hypothetically, the increased sensitivity to oral HCs in women with ADHD may be due to fluctuating hormonal levels following oral intake⁴² or during the pill-free interval. In contrast, the non-oral products result in stable serum concentrations of the contraceptive steroids.⁴² There is a considerable lack of studies on how women with ADHD respond to hormonal fluctuations, but there are several reports on how progesterone (or synthetic progestogen) fluctuations affect mood in women.⁴³ Of interest, a recent report suggested the prevalence of premenstrual dysphoric disorder and postpartum depression are high in women with ADHD compared to that in the general population.⁴⁴ Yet another possible explanation for our findings may be more specific to ADHD. Core symptoms of ADHD such as impaired cognitive function (ie, distractibility, disorganization, and impulsivity) as well as common comorbidity may

compromise consistent or correct use of ADHD medication and, potentially, adherence to contraceptive use.⁴⁵ Poor adherence to oral HC use (ie, occasionally forgetting to take a pill) increases the risk of side effects, such as irregular bleeding pattern, withdrawal bleedings, mood changes, or, ultimately, unplanned pregnancies.⁴⁶ These side effects, together with the psychological stress of becoming pregnant, may increase anxiety and place susceptible women at increased risk for depression.⁴⁶⁻⁴⁹ Thus, methods such as long-acting reversible contraception (LARCs), namely, intrauterine devices and contraceptive implants, that will be effective regardless of individual action have the potential to protect young women with ADHD against side effects and unintended pregnancies.

Our findings suggest that the use of non-oral HCs does not confer an additional risk of depression in comparison to that in women without ADHD. As women with psychiatric conditions often are effectively excluded from clinical trials on HCs, the literature so far provides limited information on the prevalence and magnitude of hormone-related adverse outcomes in girls and women with ADHD. Given the increased risk of depression in women with ADHD, which may be further increased by oral HC use, future clinical trials on contraception need to include women with mental health problems, including ADHD, to guide prescribers on the best available choices for these women.

HCs may also be used to treat women with heavy menstrual bleeding, irregular menses, dysmenorrhea, and acne. According to the literature, these conditions themselves are associated with a 2-fold increased risk of depression.⁵⁰⁻⁵² We were largely able to replicate these findings, although the estimated risks were somewhat smaller, ranging between 29% increased risk for acne to 80% increased risk in women with dysmenorrhea. Medical reasons for HC were more common in women with ADHD, further placing them at risk for depression.

Our results need to be interpreted in the context of some limitations. Around 10% of women ($n = 3,361$ of a total of 29,767 women with ADHD) were defined as having an ADHD diagnosis based on prescribed medication unique for the treatment of ADHD rather than *ICD-10* diagnoses. However, Swedish national guidelines state that medication should be reserved for ADHD cases in which other supportive interventions have failed,⁵³ indicating that this proxy identifies the most severe cases. This is further corroborated by our sensitivity analyses in women with ADHD, robust to definition according to *ICD-10* diagnoses and ATC code for ADHD medication. In addition, girls and women with ADHD are still often undiagnosed or misdiagnosed and instead commonly referred and treated for depression.⁵⁴ However, we consider that this potential

bias due to misclassification most probably would affect our results toward the null. We also acknowledge that the outcome used in this study, namely, prescription of antidepressants, does not uniquely reflect the risk of depression but rather a blend of depressive and anxiety disorders. However, sensitivity analyses showed that results were robust to different outcome definitions, that is, depression defined as *ICD* diagnosis or ATC code for antidepressants. Another caveat of this study is that large national registers may not allow for granularity of important variables that may confound the association. Indeed, we were not able to control for age at first intercourse, cigarette smoking, or body mass index, which, according to previous research, is associated with exposures (ADHD and HC use) and outcome (depression). Furthermore, given the methodological choice to focus on incident depression, that is, excluding all women with depression prior to the study start, our results cannot be generalized to women experiencing depression when seeking contraceptive counseling at youth clinics. Finally, as in all observational studies, we could not fully rule out selection bias and residual confounding due to a lack of intact information on exposures, outcome variables, and missing covariates. Importantly, however, strengths of our study include a population-based approach, with aggregated data covering the entire Swedish population in several nationwide public health registers. Since participation in Swedish government-administered registers is compulsory, selection bias is minimized.⁵⁵ Hence studies informed by population-based registers are, in contrast to trial conditions, well suited to investigate treatments in standard-of-care conditions.

ADHD is associated with age-inappropriate symptoms of disinhibition, risk taking, and somatic as well as psychiatric comorbidity,⁵⁶ causing psychosocial impairment including risk for early and unwanted pregnancies¹⁵ with adverse obstetric and perinatal outcomes.⁵⁷ To prevent subsequent unplanned pregnancies and to overcome health disparities among women, health care providers need to identify women at risk and provide them with the most-effective contraceptive methods that are easily available and that do not confer unnecessary risk of depression.

In conclusion, our findings suggest that information on risks with HCs as well as potential benefits with user-independent long-acting reversible contraception needs to be an integrated part of the shared decision making and contraception counseling for young women with ADHD.

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Pharma, Natural Cycles, Mithra, Teva, Merck, Ferring, and Consilient Health, and has provided expert opinion for Bayer, Evolan, Gedeon Richter, Exeltis, Merck, Teva, and Natural Cycles. She has been an investigator in trials sponsored by Bayer, MSD, Mithra, Ethicon, Azanta, and Gedeon Richter and has taught in courses sponsored by Merck and MSD/Organon, Bayer, and Gedeon Richter. Dr. Sundström-Poromaa has served occasionally on advisory boards or acted as invited speaker at scientific meetings for MSD, Bayer Health Care, Peptonics, Shire, and Lundbeck A/S. Drs. Sundström-Poromaa and Skoglund have reported being members of the Scientific Council at the Swedish Medical Products Agency SE-75103 Uppsala Sweden. The views expressed in this paper are not necessary the view of the Government agency. Dr. Skoglund has reported being founder and owner of a private Swedish clinic for assessment and treatment of ADHD in children and adults. She has participated at advisory boards (2016, 2022), has served as invited speaker at scientific meetings for Shire/Takeda, Nordic Drugs, UCB Pharma, DNE Pharma, Novartis, Medicie Nordic, Johnson & Johnson, Lundbeck, Gedeon Richter, and Evolan during 2016-2021, has served as an investigator for two studies funded by Takeda 2021-2022, and has taught in courses sponsored by Takeda. Drs. Lundin, A. Wikman, and P. Wikman have reported no biomedical financial interests or potential conflicts of interest.

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