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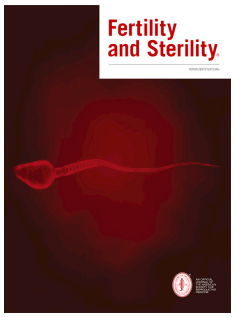

Anti-Müllerian hormone levels are associated with time to pregnancy in a prospective cohort study of 3,150 women

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Running Title: AMH and time to pregnancy

Article Title: Anti-Müllerian hormone levels are associated with time to pregnancy in a prospective cohort study of 3,150 women

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MS nothing to disclose.

BJE is a prior employee of Modern Health Inc.

AV is the founder of Modern Health Inc. and owns stock in the company.

KM is a full-time employee of Modern Health Inc. and owns stock in the company.

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Capsule: Low AMH levels (<1 ng/ml) are independently associated with a modest reduction in the chance of natural conception.

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Structured Abstract

Objective: To study the association between AMH and time to pregnancy. While it has been hypothesized that serum anti-Müllerian hormone (AMH) levels may indicate the chance of conception, findings have been mixed. Given that any association is expected to be modest, and it is possible that previous studies have been underpowered, we investigated this relationship in the largest prospective cohort to date.

Design: Prospective time-to-pregnancy cohort study.

Subjects: 3,150 US women who had been trying to conceive for less than 3 months and had purchased a Modern Fertility Hormone Test.

Exposure: We developed a discrete time-to-event model utilizing a binomial complementary log-log error structure within a generalized additive modeling framework, adjusting for confounding factors such as age, BMI, parity, smoking status, PCOS, and others. Sensitivity analyses were performed in women with regular menstrual cycles (21-35 days), who did not report using fertility treatments, using alternate AMH categories (<0.7, 0.7-8.5, >8.5 ng/mL), and AMH as a continuous measure.

Main Outcome Measures: Primary outcomes included cumulative conception probability within 12 cycles and relative fecundability per menstrual cycle. Conception was defined by a self-reported positive pregnancy test.

Results: Participants contributed 7.21 ± 5.32 cycles, with 1,325 (42.1%) achieving a pregnancy. Women with low AMH (<1ng/mL, n=427) had a lower chance of natural conception (Adjusted Hazard Ratio (adjHR 0.77, 95%CI 0.64, 0.94, p=0.009) compared to women with a normal AMH (1 - 5.5ng/mL). There was no difference between high (5.5+ ng/ml) and normal AMH categories (adjHR 1.11, 95% CI 0.94, 1.31, p=0.2). The inclusion of AMH improved the model (net reclassification index 0.10 [0.06 - 0.14); P<0.001). The instantaneous probability of conception was highest in cycle 4 across all AMH categories: the probability of natural conception was 11.2% (95% CI 9.0, 14.0) for low AMH, 14.3% (95% CI 12.3, 16.5) for normal AMH, and 15.7% (95%CI 12.9, 19.0) for high AMH. In the regular cycles sensitivity analysis (n=1,791), the low AMH group had a lower chance of conception (adjHR 0.77 95% CI 0.61, 0.97, p = 0.028) in the

low AMH group compared to normal AMH, and similarly in the continuous model (adjHR 0.90; 95% CI 0.85-0.95, p<0.0001).

Conclusion: Low AMH levels (<1 ng/ml) are independently associated with a modest but significant reduction in the chance of conception.

Keywords: AMH, ovarian reserve, conception, fecundity, pregnancy.

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Introduction

Changes in global social and cultural expectations have led to a trend of delayed childbearing, especially in the United States (1). As a result, an increasing number of people are proactively pursuing information about their ovarian reserve and potential fertility window, especially when deciding when and how to start a family (2-4). Anti-Müllerian hormone (AMH) is increasingly recognized as the best available biomarker of functional ovarian reserve, reflecting its associations with primordial follicle counts (5), treatment outcomes such as the response to ovarian stimulation (6, 7) and time to menopause (8).

At this juncture, the American College of Obstetrics and Gynecologists (ACOG) has determined that there is insufficient evidence for clinicians to use AMH for counseling patients with untested fertility. Specifically, they say “a single serum anti-müllerian hormone level […] does not appear to be useful in predicting time to pregnancy and should not be used for counseling patients in this regard” (9). This perspective is based on several studies that found no association between serum AMH levels and time to pregnancy (10-12), along with a broader body of literature that has been inconsistent in quantifying the association between AMH and fecundity. Some of this research suggests a positive association (13, 14) with improved net reclassification by including AMH (15), and others research shows no effect (16, 17).

A highly cited paper in this field, Steiner et al. (2017), reported no association with positive pregnancy rates (10). However, subsequent analysis of the same cohort showed an association of low AMH with miscarriage (18), consistent with systematic reviews and meta-analysis (19). It is possible that these results are specific to the unique patient population, or study design or that the study may have been underpowered to detect a significant effect. In fact, a systematic review of 11 studies and 4,388 women suggested a weak predictive value of AMH for spontaneous pregnancy (20). In in-vitro fertilization (IVF), where there are substantially larger analyses, a recent systematic review found the effect estimates of association with AMH and live birth are similarly weak. Still overall AMH has consistently been shown to be associated with live birth independent of ovarian response and age (21, 22).

Similarly modest effects are likely in the context of a population with unknown fertility. However, substantially larger sample sizes than have been investigated to date may be required to

robustly detect these modest effects. To explore this further, we assessed AMH values across reproductive ages in a large US population who report trying to conceive.

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Materials and Methods

Study design and Participants

Study participants were selected from Modern Fertility (San Francisco, CA) customers between the ages of 21 and 45, who had submitted a blood sample between August 2018 and March 2023. Modern Fertility offers fertility hormone testing for people with ovaries who want to become pregnant one day or are generally curious about their fertility hormones. Blood is collected via an at-home collection kit or via Quest blood draw and the lab results are returned in a digital patient portal along with educational content. Modern Fertility also offers a free iOS cycle-tracking app.

To be eligible for this study, participants must have tracked their cycles in the Modern Fertility app, been trying to conceive, and reported when they started trying to conceive (month, year) either via app or digital questionnaire. Only those participants who collected a blood sample no later than three months after they started trying to conceive were included.

Participants who self-reported a previous diagnosis of a specific gonadal disorder/dysfunction (amenorrhea, oligomenorrhea, gonadal congenital abnormalities) or prior diagnosis of premature ovarian insufficiency were excluded (Supplemental Figure 1). Those who self-reported a diagnosis of polycystic ovary syndrome but did not report oligomenorrhea, were included.

Baseline demographic data was self-reported via digital questionnaire and included height, weight, smoking status, race/ethnicity, previous pregnancies, use of assistance while trying to conceive (participants were asked whether they were “trying for kids as we speak (without assistance)” or “trying for kids as we speak (with fertility treatment)”). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Participants self-identified as American Indian or Alaskan, White, Black or African American, Hispanic or Latino, Asian, Native Hawaiian or Pacific Islander, or “other.” Individuals who self-identified as more than one race/ethnicity were considered of multi-race/ethnicity. The questions answered by patients were built into the product experience and were not specific to this study.

All participants provided informed consent to participate in the research with all data de-identified prior to analysis. The informed consent did not explicitly describe the study or studies that would be done with the data (broad consent) and participants were not explicitly aware that their data would be analyzed for a time-to-pregnancy study. The consent rate of Modern Fertility customers to the broader consent was approximately 65%. This study was approved by the Western Institutional Review Board, protocol number 20180443, an ethics committee that ensures proper research consent and methodology are followed.

Cycle Data Cleaning

In our analysis, we applied left and right censoring techniques to the cycle tracking data to ensure comprehensive analysis of the dataset, even in instances where complete data collection was not feasible.

Left censoring was determined by identifying the start of the first recorded menstrual cycle within the timeframe set for conception attempts. This involved calculating the interval between each self-reported menstruation day in the tracking application. Consecutive entries with intervals of 14 days or more were classified as separate menstrual cycles.

Right censoring was employed in cases where the interval between data entries exceeded 46 days, suggesting a potential unrecorded conception event. In such instances, subsequent cycles post the 46-day gap were excluded from the analysis. The median cycle length was derived from observed cycle lengths that did not exceed this 46-day threshold. This median, along with the difference between the specified start date for trying to conceive (TTC) and the date of the first recorded cycle, was used for estimating the adjusted start cycle for left censoring. Additionally, instances where subjects exceeded two years of data submission or where the interval between consecutive data points surpassed 46 days were also categorized as right censored.

AMH measurement

All Modern Fertility customers are instructed to collect a blood sample on day 3 of their menstrual cycle; if they do not menstruate, they are instructed to collect any day. Blood samples were collected by means of one of the following methods depending on the participants

preference: (1) dried blood spot collection card processed by US Specialty Labs (San Diego, CA); or (2) venipuncture processed at Quest Diagnostics (Secaucus, NJ). Both laboratories used Access AMH immunoassay by Beckman-Coulter (Brea, CA) that has a reportable measuring range of 0.08 to 24 ng/mL; limit of detection ≤0.02 ng/mL; limit of quantitation ≤0.08 ng/mL) (23). All samples were analyzed continuously throughout the study period. For the dried blood spot samples, four large drops of blood were collected on serum separator cards. After drying completely, the cards were mailed to the laboratory for processing. The coefficient of variation varies from 3.3% to 4.5% as previously reported (24). Because previous work has demonstrated that AMH levels are stable only for up to 14 days, any samples received after the 14-day window were not processed and a new sample was collected (25). Validation studies suggest excellent concordance between dried blood spot and venipuncture sampling for AMH ($r>0.97$) and no statistically significant bias, suggesting that AMH values from these two methods can be used and interpreted interchangeably (24, 25). For the analysis, values below the assay limit of quantitation were classed as 0.079ng/ml and included.

Statistical analysis

The primary outcome measure for the study was the cumulative probability of conception after 12 menstrual cycles. We allowed the relationship between predictors and fecundability to include nonlinear relationships between AMH, age, and BMI. To maintain power in the analysis, we preserved the non-linearity for age and BMI by not further categorizing these continuous predictors. To make the interpretation of AMH consistent with previous studies and to maximize the utility of our findings in a clinical setting, we categorized AMH into low, normal, and high categories. We also included a sensitivity analysis that treated AMH as continuous measure.

Our choice of cut points was intended to incorporate those used in prior publications and in current clinical use, and to ensure a balance between our high and low AMH categories (26–28). AMH levels were thus classified for this analysis as low (<1.00 ng/mL), normal (1.00 - <5.5 ng/mL), and high (≥5.5 ng/mL)(12). We also replicated the analysis, using previously published thresholds by Steiner and colleagues of low (<0.7 ng/mL), normal (0.7 - 8.4 ng/mL), and high (≥8.5 ng/mL)(10).

We chose a discrete-time model to account for differences in menstrual cycle length between participants. We chose a discrete Cox proportional hazards regression for time-to-event

modeling. This approach accounts for both left and right censoring which is necessary because participants entered at different points in their attempts to conceive (left-censored) and some did not have either 12 observed cycles or a positive pregnancy test (right-censored). Thus, cycles from enrollment to censoring were included in the analysis. Because time in these models is measured by menstrual cycles (and not chronologic time) the hazard ratios (HRs) are referred to as fecundability ratios, which are the relative probability of pregnancy in a given cycle for the exposed group relative to the reference group. In such models an HR of less than 1 suggests reduced fecundability in the exposed (or nonreferent) group.

All models were adjusted for age as a continuous non-linear variable. In line with current clinical evidence on AMH and age-related decline, we included an interaction between AMH categories and the non-linear age variable to account for any variability in AMH across the age distribution of the cohort. To test for an interaction on AMH by age, a likelihood ratio test was used to compare the fit for the model without the interaction term with that of the model including the interaction term, with a non-linear interaction between AMH and age incorporated into the final model. The analyses were additionally adjusted for body mass index as a continuous variable, current smoking status (yes or no), gravidity (ordinal and then ≥7), history of chlamydia (yes or no), endometriosis (yes or no), hypothyroidism (yes or no), polycystic ovarian syndrome (yes or no), or trying to conceive with assistance (yes or no). Cumulative event rate curves with 95% confidence intervals were also constructed. These are equivalent to 1- Kaplan Meier estimates. We also performed sensitivity analyses, restricting only to those participants who reported regular cycles, and those who reported trying to conceive without assistance.

The underlying adjusted hazard from the discrete-time Cox proportional hazard model was also assessed and can be interpreted as the instantaneous probability of conception for a given cycle. More specifically this is a modeled trend of incidence of conception over the cycle time for the cohort. To summarize the non-linear interaction between AMH and age, both the estimated cumulative conception rate and the instantaneous probability of conception at 12 cycles have been cross-tabulated using expected marginalized means.

Finally, to quantify the utility of AMH in the model, we performed a chi-squared test of deviance, net reclassification improvement (26, 27), and integrated discriminant improvement (28). For each of these tests, we compared a model with the categorized AMH removed and the full

model as described previously. All analyses were conducted using R (Version 4.2.0), R Foundation for Statistical Computing.

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Results

A total of 3,150 participants met the inclusion criteria, with a median age of 31.5 years (interquartile range (IQR) 28.5, 34.5) and AMH of 2.71 ng/ml (IQR 1.51, 4.46). Of these, 1,325 (42.1%) achieved pregnancy during follow-up (note that not all participants had 12 cycles of data, mean 7.21 ± 5.32 cycles). Women who achieved a pregnancy were more likely to be younger, have higher AMH values, have slightly lower BMI, and have no diagnosis of PCOS (Table 1).

We then modeled time-to-pregnancy and identified multiple predictors associated with the chance of conception. The chance of conceiving decreased with increasing maternal age and BMI in a non-linear manner (Table 2). With respect to AMH categories, women with low AMH (n=427, <1ng/mL) had a lower chance of conception (Adjusted Hazard Ratio (adjHR) 0.77, 95%CI 0.64, 0.94, p=0.009) compared to women with a normal AMH (Figure 1a). There was no difference between high and normal AMH categories (adjHR 1.11, 95% CI 0.94, 1.31, p=0.2) (Figure 1a, Table 2). The likelihood ratio test for interaction between the non-linear age and each of the respective AMH categories were all non-significant.

The cumulative probability of conceiving for different age and AMH categories at 6 and 12 cycles are shown in Table 3. For any given AMH category, the probability of concepton decreases as age increases. Generally, within each age category, cumulative probability of conception increases as AMH category increases. The <30 age group is the exception, where normal AMH is associated with the highest cumulative probability of conception.

We then evaluated the underlying instantaneous probability of conception at 6 and 12 cycles. We observed the highest probability of conception in cycle four regardless of AMH category (Figure 1c). The probability of conception in cycle four increases as the AMH category increases: probability was 11.2% (95% CI 9.0, 14.0) for low AMH, 14.3% (95% CI 12.3, 16.5) for normal AMH, and 15.7% (95%CI 12.9, 19.0) for high AMH. Low AMH was associated with a lower chance of conceiving across all cycles compared to normal AMH. The instantaneous probability of conception for cycles 6 and 12 of trying is shown in Table 3. We observe the same independent relationships of age and AMH on cumulative conception rate, such that within a given AMH category, the probability of conception decreases as age increases.

To further probe the strength of the association, we completed a number of additional analyses. First, we demonstrated that the model was improved by the inclusion of AMH using a chi-squared test of deviance (p = 0.012). The inclusion of AMH in the model improved the net reclassification index (NRI 0.10 [0.06 - 0.14); P<0.001) and the integrated discriminant improvement (IDI 0.0006 95%CI 0.0001 - 0.001; p = 0.023).

Second, we performed four sensitivity analyses. First, we analyzed the subset of participants with regular menstrual cycles, defined as 21 to 35 days (n=1,791). The chance of conception was also lower (adjHR 0.77, 95% CI 0.61, 0.97, p=0.028) in the low AMH group compared to normal AMH (Figure 1b, Table 2). This relationship was similar when comparing the instantaneous probability of conception (Figure 2d). Second, we analyzed the subgroup restricted to women who did not self-report any assistance while trying to conceive (n=2,972). We observed that the chance of conception was lower in the low AMH group compared to normal AMH (adjHR 0.77 95% CI 0.61, 0.97, p = 0.028) (Supplemental Table 1, Supplemental Figure 2a). Third, we repeated the main analysis using previously reported AMH categories (low AMH <0.7 ng/ml (n=256 women)). The association was not significant (adjHR 0.93; 95%CI 0.73, 1.17, p = 0.5), which may be due to the smaller group size of low AMH participants resulting in a wider confidence interval (Supplemental Table 1, Supplemental Figure 2b). Instantaneous probability of conception for the no assistance subset and the alternate AMH categories analyses are in Supplemental Figure 3. Lastly, when we performed the analysis with AMH as a continuous measure with marginalization of the AMH categories, the results were similar with a lower chance of conception with low AMH (<1ng/ml) (adjHR 0.90; 95% CI 0.85-0.95, p<0.0001).

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Discussion

In this large prospective cohort study of women trying to conceive, we identify that a low AMH is negatively associated with time to pregnancy, such that women with an AMH <1ng/ml will take ~20% longer to conceive. This association is independent of other classical factors such as age and time spent trying to conceive. These findings persist in our sensitivity analyses of women with regular menstrual cycles and among those trying to conceive without assistance, which further adds to the robustness of our findings. We identify that the chance of conception peaks within the first few months of trying to conceive, with a gradual decline thereafter, and that this is consistent across AMH categories. For some women with a low AMH, earlier referral for further investigations may be warranted.

Our findings are clinically important because, despite the mixed results of previous studies, the prevailing clinical consensus is that AMH is not relevant to time to pregnancy in a presumed fertile population. In fact, Steiner's landmark study is often cited as evidence that there is no association between serum AMH levels and the chance of conception (10) and has also played a role in ACOG's recommendations against AMH testing in populations with presumed fertility (9). Despite this recommendation, some prior studies show a modest effect of AMH on time to pregnancy (13-15). These prior studies have been comparatively small (n<500), used different study designs, and had different inclusion criteria. A prior meta-analysis of 11 studies and 4,388 women also found a moderate effect of AMH on chance of conceiving (20). Our findings, alongside this prior body of work, challenge the long-held belief that AMH is not relevant in a population with unknown fertility.

The biological mechanisms that could explain the association between low AMH and reduced chance of conceiving are currently largely speculative. Some authors have suggested that there may be an association between low ovarian reserve markers including AMH and increased risk of aneuploid embryos (29, 30). Large population studies suggest that AMH is independently associated with live birth in both fresh and frozen-thawed embryo transfer cycles (21, 31) and with the probability of obtaining a euploid embryo (32), supporting the concept that there may be a quantitative and qualitative effect. Although AMH declines with age, for young women with an inappropriately low AMH this may reflect more rapid ovarian aging and with that, a higher risk of early menopause (8, 33). Consistent with this concept of earlier aging, genome-wide associations studies assessing AMH identified multiple loci involved in the cell cycle and

processes such as DNA replication and apoptosis (34). As AMH is predominantly produced by granulosa cells of small antral follicles, whether it is also a potential marker of granulosa cell function and the quality of ovulation is unclear (35). It is increasingly recognized that there is potential variability in the development of dominant follicles and corpus luteal function (36). Lastly, low AMH may be a marker of other unmeasured factors, such as socioeconomic status or comorbidities that could adversely impact on the chance of conceiving (37, 38).

While our study has several strengths including its size and the reproducibility of the principal findings in women with regular menstrual cycles, we do acknowledge several limitations. The participants were all customers of Modern Fertility, and therefore, there may be selection bias, particularly with respect to socioeconomic status and environmental, lifestyle, reproductive, or early childhood factors that may impact their chance of conceiving. The observed number of pregnancies was lower than reported for other natural conception cohorts, which is likely due to under-reporting within the cycle tracking app but may reflect an inherent difference in our population. As participants were also using the cycle tracking app for their own personal use, and not for an explicit time-to-pregnancy study, it is possible that they might not have recorded a positive pregnancy test or may have had a positive pregnancy test but experienced an early pregnancy loss and decided not to record this information. We used a multi-ethnic population, but ethnicity was not reported for 46% of the participants and so we were unable to account for this in the multivariable model. We do not have demographic or clinical details on male partners and appreciate that some of these men may subsequently be determined to be oligo or azoospermic. However, this reflects clinical reality, where many couples would not have semen analysis until they have been trying to conceive for 6 or 12 months, consistent with national guidelines (39). We acknowledge that we could not control for the recency of contraceptive use (40). However, the effect on AMH concentrations is dependent on the mode of contraception (41), and for women using the combined oral contraceptive pill which shows the greatest effect on AMH concentrations, values return to normal within 2 months (42). Importantly, the intention of our modeling was not for clinical prediction of conception as defined by the TRIPOD statement (43), as alternative validated models exist (38, 39), but rather to understand the association of AMH with the estimated probability of conception. Future fecundity prediction models may explore whether the incorporation of AMH minimizes prediction error and enhances clinical decision-making. Alternative mathematical approaches including more flexible models within the Cox framework or accelerated failure time models could be utilized in further studies, subject to external validation of our findings. Similarly our use of NRI and IDI for model

assessment was solely to assess their contribution to our principal model, as their limitations, particularly of NRI in risk-prediction instruments, are well recognized (27). We acknowledge that we have not undertaken causal inference and future studies could be designed to assess the causal estimand. Lastly, we do not have pregnancy outcome data, and further studies should assess the association of AMH with live birth given the known weak association of low ovarian reserve as determined by both AMH and antral follicle count with the incidence of miscarriage (19) and recurrent pregnancy loss (44).

Our model is not designed to determine access to care or drive patients to immediate infertility assessment, with other validated models already available for this purpose (45, 46). Rather, our study was developed to assess whether there was a modest but measurable association between AMH and the chance of conception, counter to commonly accepted dogma. Previously conducted studies that did not find an association may have been underpowered to detect it or may have utilized a broader range of AMH values to define “abnormal” findings, thus obscuring significant results. For patients with unknown fertility who desire a proactive assessment of their chance of conception, it is not unreasonable to consider drawing a serum AMH as part of a standard preconception panel. That AMH result could be used as one clinically relevant piece of information, among others, when counseling those patients regarding a potential timeline for attempting conception.

Conclusion

Our large prospective study confirms that a low AMH (<1 ng/mL) is associated with a reduced chance of conceiving at all ages. We anticipate that this information, in conjunction with the extensive body of literature on factors influencing fecundity, can serve to proactively counsel patients and help women better plan their reproductive timeline.

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The authors would like to thank all Modern Fertility customers who agreed to participate in the research, which made this study possible.

Conflicts of Interest

SMN has participated in Advisory Boards and received speakers or consultancy fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, MSD, Roche Diagnostics and The Fertility Partnership. SFB is an employee of Modern Fertility. SFB, AV, and BJE have stock options in the company. Modern Fertility paid salaries and consulting fees for the time the authors spent working on this project.

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Figure Legend

Figure 1. Predicted time to pregnancy and instantaneous probability of conception by cycle

Top panel (A and B): Predicted time to pregnancy
Discrete predicted time to model for pregnancy for all participants (A) and participants with regular menstrual cycles (B), with cumulative pregnancy rates through to 12 months.

Lower Panel (C and D): Instantaneous probability of conception by cycle
Individual probability of pregnancy in a specific cycle for all participants (C) and participants with regular menstrual cycles (D) through to 12 months

For convenience the figures are shown here in addition to being uploaded separately.

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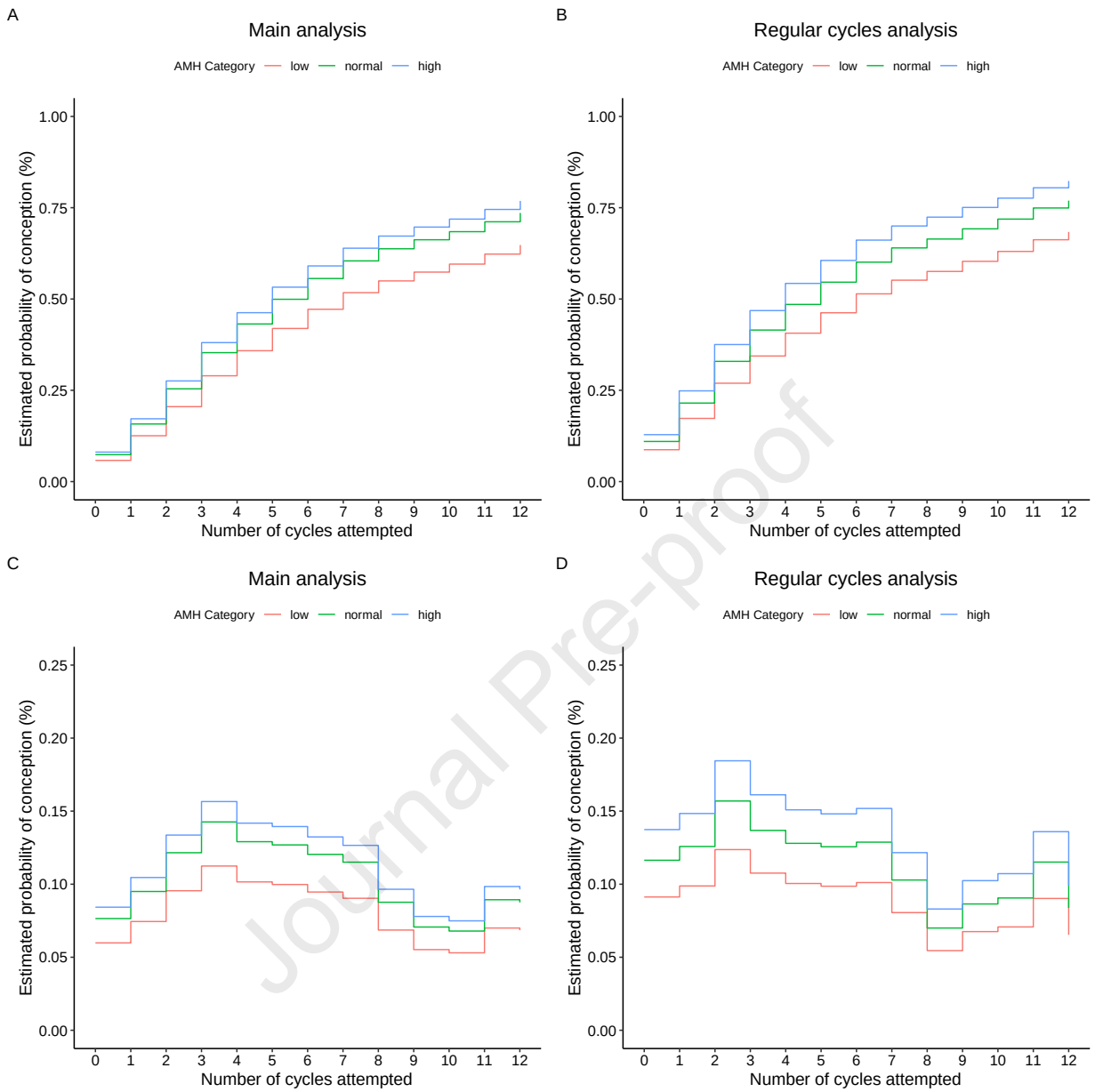

Figure 1. Predicted time to pregnancy and instantaneous probability of conception by cycle

Top panel (A and B): Predicted time to pregnancy
Discrete predicted time to model for pregnancy for all participants (A) and participants with regular menstrual cycles (21 – 35 days) (B), with cumulative pregnancy rates through to 12 months.
Lower Panel (C and D): Instantaneous probability of conception by cycle
Individual probability of pregnancy in a specific cycle for all participants (C) and participants with regular menstrual cycles (21 – 35 days) (D) through to 12 months

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Table 1: Participant Characteristics

Characteristic	Overall (n = 3,150)[1]	Positive Pregnancy Test (n = 1,325)[1]	Negative Pregnancy Test (n = 1,825)[1]	p-value[2]
AMH value (ng/ml)	2.71 (1.53, 4.53)	2.89 (1.65, 4.60)	2.54 (1.40, 4.33))	<0.001
BMI (kg/m^2)	25 (22, 31)	24 (22, 29)	26 (22, 32)	<0.001
Gravidity				0.088
0	2,346 (74%)	1,026 (77%)	1,320 (72%)	
1	437 (14%)	173 (13%)	264 (14%)	
2	195 (6.2%)	70 (5.3%)	125 (6.8%)	
3	82 (2.6%)	26 (2.0%)	56 (3.1%)	
4	36 (1.1%)	10 (0.8%)	26 (1.4%)	
5	27 (0.9%)	10 (0.8%)	17 (0.9%)	
6	12 (0.4%)	5 (0.4%)	7 (0.4%)	
7+	15 (0.5%)	5 (0.4%)	10 (0.5%)	
Ethnicity				0.015
White	1,245 (40%)	567 (43%)	678 (37%)	
American Indian / Alaskan	41 (1.3%)	11 (0.8%)	30 (1.6%)	
Asian	87 (2.8%)	36 (2.7%)	51 (2.8%)	
Black / African American	83 (2.6%)	29 (2.2%)	54 (3.0%)	
Hispanic / Latino	167 (5.3%)	61 (4.6%)	106 (5.8%)	
Native Hawaiian / Pacific Islander	4 (0.1%)	2 (0.2%)	2 (0.1%)	
Unknown	1,523 (48%)	619 (47%)	904 (50%)	
Chlamydia	197 (6.3%)	78 (5.9%)	119 (6.5%)	0.5
Endometriosis	68 (2.2%)	29 (2.2%)	39 (2.1%)	>0.9
Hypothyroidism	189 (6.0%)	73 (5.5%)	116 (6.4%)	0.3
PCOS	192 (6.1%)	69 (5.2%)	123 (6.7%)	0.076
TTC Assistance	178 (5.8%)	64 (4.9%)	114 (6.4%)	0.074
Missing	82	25	57	
AMH Categories (ng/ml)				<0.001
Normal (1 - 5.5)	2,219 (70%)	981 (74%)	1,238 (68%)	
Low (<1)	427 (14%)	134 (10%)	293 (16%)	
High (5.5+)	504 (16%)	210 (16%)	294 (16%)	
Alternate AMH Categories (ng/ml)[3]				0.001
Normal (0.7 - 8.5)	2,744 (87%)	1,179 (89%)	1,565 (86%)	
Low (<0.7)	256 (8.1%)	80 (6.0%)	176 (9.6%)	
High (8.5+)	150 (4.8%)	66 (5.0%)	84 (4.6%)	
Age at TTC start (years)	31.5 (28.8, 34.5)	31.1 (28.5, 33.9)	31.8 (28.9, 35.1)	<0.001
Smoker	135 (4.3%)	47 (3.5%)	88 (4.8%)	0.081

[1]Median (IQR); n (%)

[2]Wilcoxon rank sum test; Fisher's Exact Test for Count Data with simulated p-value (based on 2000 replicates); Pearson's Chi-squared test

[3]Steiner 2017

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Table 2: Association of baseline characteristics with cumulative probability of conception

	Main Analysis			Regular Cycles Analysis		
Characteristic	**HR[1]**	**95% CI[1]**	**p-value**	**HR[1]**	**95% CI[1]**	**p-value**
AMH Categories						
Normal (1 - 5.5)	—	—		—	—	
Low (<1)	0.77	0.64, 0.94	0.009	0.77	0.61, 0.97	0.028
High (5.5+)	1.11	0.94, 1.31	0.2	1.19	0.98, 1.46	0.082
Chlamydia	0.79	0.62, 0.99	0.042	0.87	0.66, 1.14	0.3
Endometriosis	1.27	0.87, 1.85	0.2	1.14	0.67, 1.94	0.6
Hypothyroidism	1.00	0.79, 1.28	>0.9	1.02	0.74, 1.40	>0.9
Smoker	0.75	0.55, 1.02	0.067	0.59	0.39, 0.90	0.015
PCOS	0.89	0.69, 1.14	0.4	0.87	0.63, 1.20	0.4
TTC assistance	0.60	0.46, 0.77	<0.001	0.61	0.44, 0.86	0.005
Gravidity						
0	—	—		—	—	
1	1.11	0.94, 1.31	0.2	1.12	0.91, 1.39	0.3
2	1.23	0.96, 1.58	0.10	1.35	0.98, 1.86	0.067
3	1.21	0.81, 1.79	0.4	1.16	0.70, 1.91	0.6
4	1.01	0.54, 1.90	>0.9	0.59	0.22, 1.58	0.3
5	1.54	0.81, 2.90	0.2	1.33	0.58, 3.00	0.5
6	1.74	0.72, 4.20	0.2	1.89	0.78, 4.58	0.2
7+	1.15	0.43, 3.10	0.8	1.56	0.50, 4.84	0.4
Cycle Number						
0	—	—		—	—	
1	1.26	0.82, 1.93	0.3	1.09	0.68, 1.73	0.7
2	1.63	1.08, 2.45	0.020	1.38	0.89, 2.14	0.2
3	1.93	1.29, 2.91	0.002	1.19	0.76, 1.86	0.5
4	1.74	1.15, 2.63	0.009	1.11	0.70, 1.75	0.7
5	1.71	1.12, 2.60	0.013	1.08	0.68, 1.73	0.7
6	1.61	1.05, 2.48	0.029	1.11	0.69, 1.79	0.7
7	1.54	0.99, 2.39	0.056	0.88	0.53, 1.46	0.6
8	1.15	0.72, 1.85	0.6	0.59	0.33, 1.03	0.065
9	0.92	0.56, 1.53	0.8	0.73	0.42, 1.27	0.3
10	0.88	0.52, 1.49	0.6	0.77	0.44, 1.35	0.4
11	1.18	0.71, 1.95	0.5	0.99	0.57, 1.72	>0.9
12	1.15	0.68, 1.95	0.6	0.71	0.38, 1.32	0.3
13	1.14	0.66, 1.97	0.6	0.59	0.29, 1.18	0.14
14	0.92	0.50, 1.70	0.8	0.53	0.25, 1.15	0.11
15	0.83	0.43, 1.62	0.6	0.95	0.48, 1.87	0.9
16	1.18	0.63, 2.24	0.6	0.70	0.31, 1.57	0.4
17	0.71	0.32, 1.57	0.4	0.30	0.09, 0.99	0.048
18	0.70	0.30, 1.62	0.4	0.23	0.06, 0.99	0.049
19	0.25	0.06, 1.04	0.057	0.82	0.33, 2.02	0.7
20	0.88	0.36, 2.14	0.8	0.70	0.24, 2.04	0.5
21	0.75	0.26, 2.14	0.6	0.40	0.09, 1.69	0.2
22	0.47	0.11, 1.96	0.3	0.24	0.03, 1.82	0.2
23	0.28	0.04, 2.06	0.2	0.82	0.25, 2.76	0.8
24	0.98	0.30, 3.26	>0.9	1.36	0.47, 3.92	0.6

[1]HR = Hazard Ratio, CI = Confidence Interval

[2]Age = the age at start of trying to conceive (TTC)

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Reference categories for Chlamydia, Endometriosis, Hypothyroidism, PCOS, Smoking status and TTC assistance are participants who report “no” for each of those.
Age and BMI were considered non-linear covariates in the model using a thin plate regression spline.

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Table 3: Age and AMH stratified instantaneous and cumulative pregnancy rates at and through to 6 and 12 cycles

	Instantaneous pregnancy rate					
	At cycle 6			At cycle 12		
	Low AMH	Normal AMH	High AMH	Low AMH	Normal AMH	High AMH
<30 yrs	0.10 (0.07-0.143)	0.12 (0.09,0.16)	0.12 (0.08-0.16)	0.07 (0.05-0.11)	0.09 (0.06-0.13)	0.08 (0.05-0.13)
30 - <35 yrs	0.08 (0.06-0.10)	0.10 (0.08-0.12)	0.11 (0.08-0.14)	0.06 (0.04-0.08)	0.07 (0.05-0.10)	0.08 (0.05-0.11)
35 - <38 yrs	0.06 (0.04-0.08)	0.08 (0.06-0.1)	0.09 (0.07-0.13)	0.04 (0.03-0.06)	0.06 (0.04-0.08)	0.07 (0.0,0.11)
38+ yrs	0.03 (0.02,0.04)	0.03 (0.02,0.04)	0.05 (0.03,0.08)	0.02 (0.01,0.03)	0.03 (0.02,0.04)	0.04(0.02,0.04)
	Cumulative pregnancy rate					
	After 6 cycles			**After 12 cycles**		
	Low AMH	Normal AMH	High AMH	Low AMH	Normal AMH	High AMH
<30 yrs	0.48 (0.38-0.59)	0.57 (0.47-0.66)	0.53 (0.42-0.65)	0.66 (0.53-0.78)	0.74 (0.63-0.84)	0.55 (0.43-0.66)
30 - <35 yrs	0.4 (0.32-0.49)	0.48 (0.41-0.56)	0.51 (0.42-0.6)	0.57 (0.46-0.68)	0.66 (0.56-0.75)	0.70 (0.59-0.80)
35 - <38 yrs	0.33 (0.26-0.41)	0.4 (0.33-0.48)	0.47 (0.37-0.59)	0.48 (0.38-0.59)	0.57 (0.47-0.67)	0.63 (0.50-0.76)
38+ yrs	0.18 (0.12-0.25)	0.22 (0.16-0.30)	0.28 (0.17-0.44)	0.27 (0.19-0.38)	0.33 (0.24-0.46)	0.42 (0.26-0.61)

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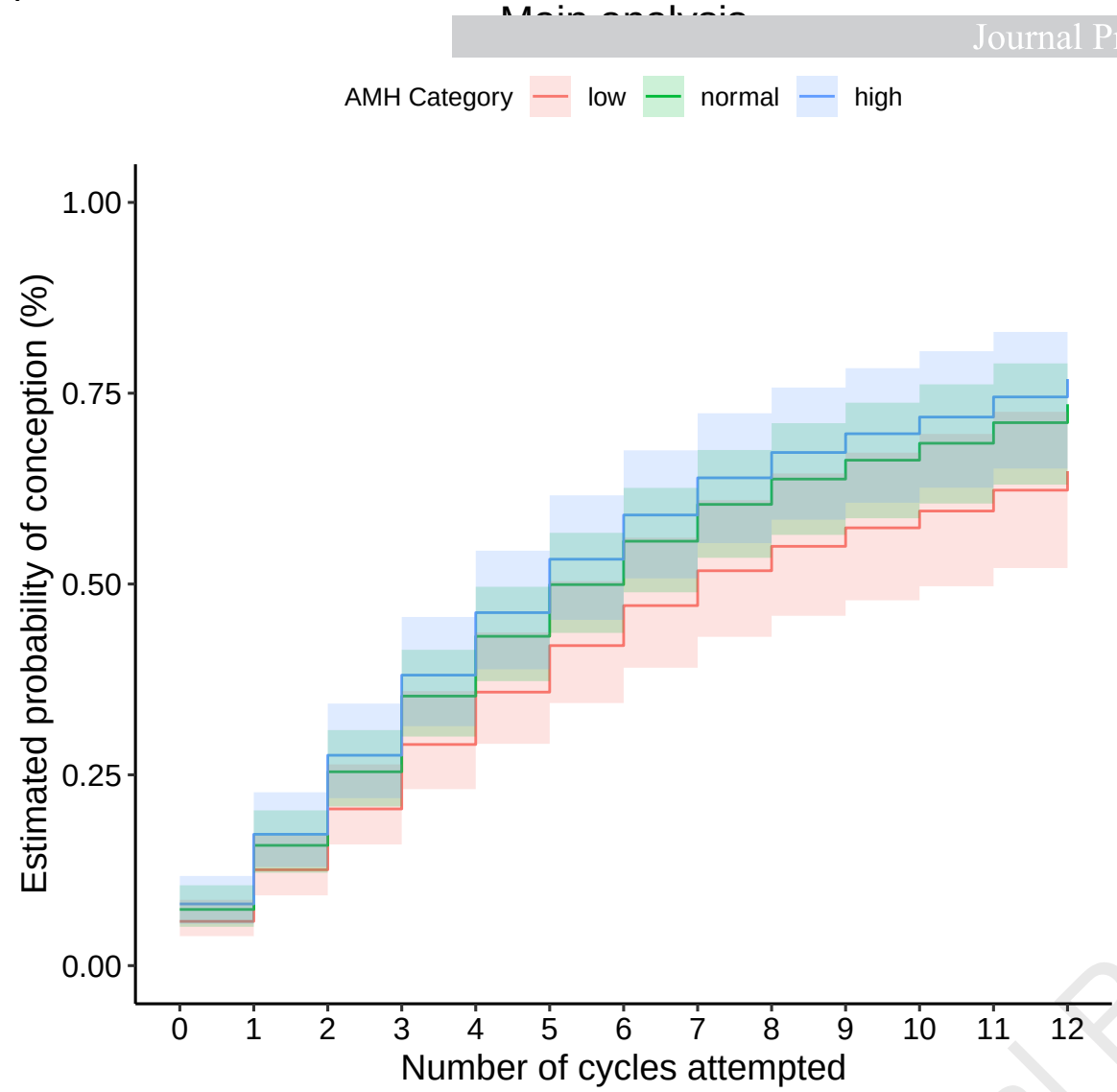

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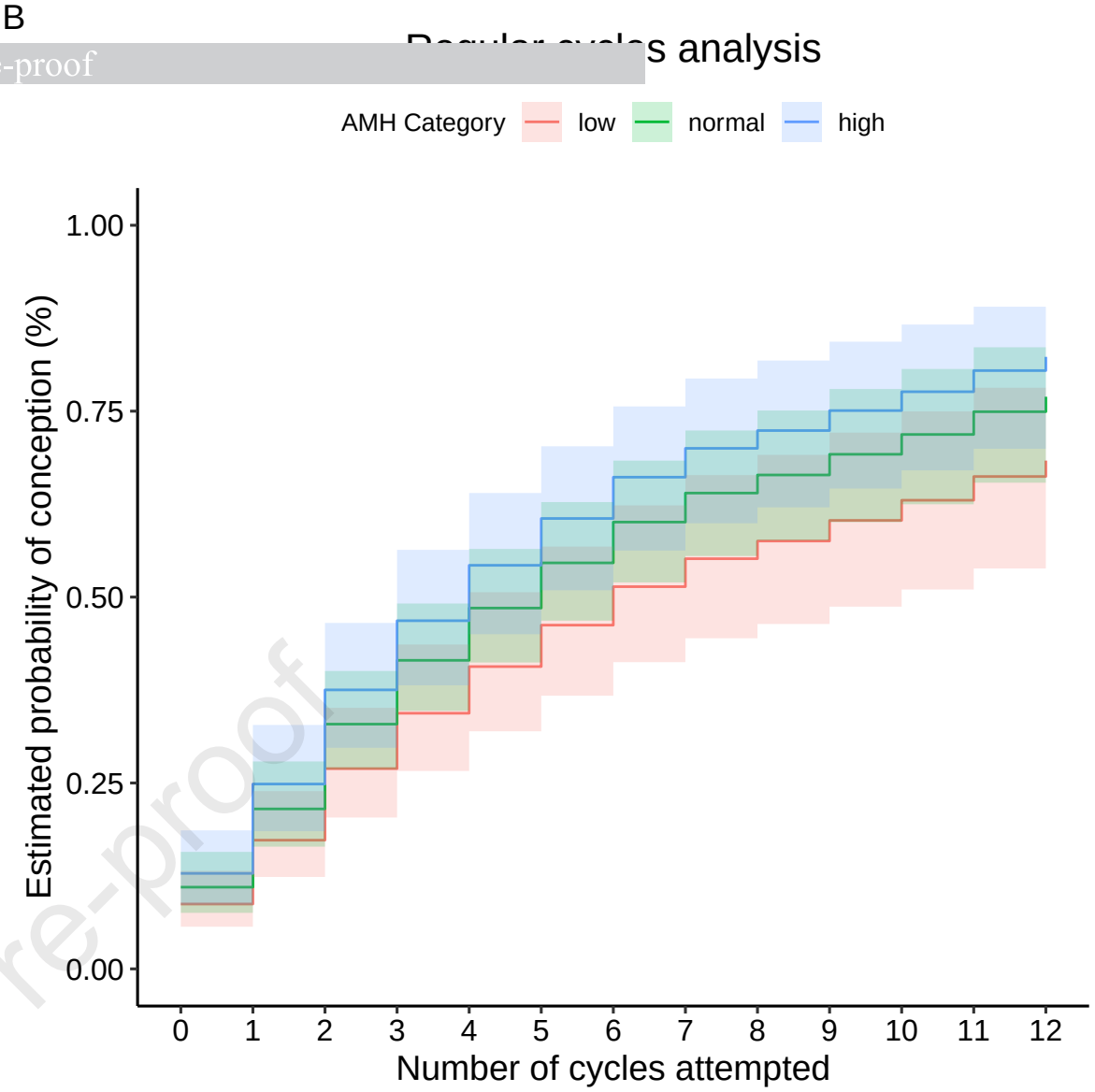

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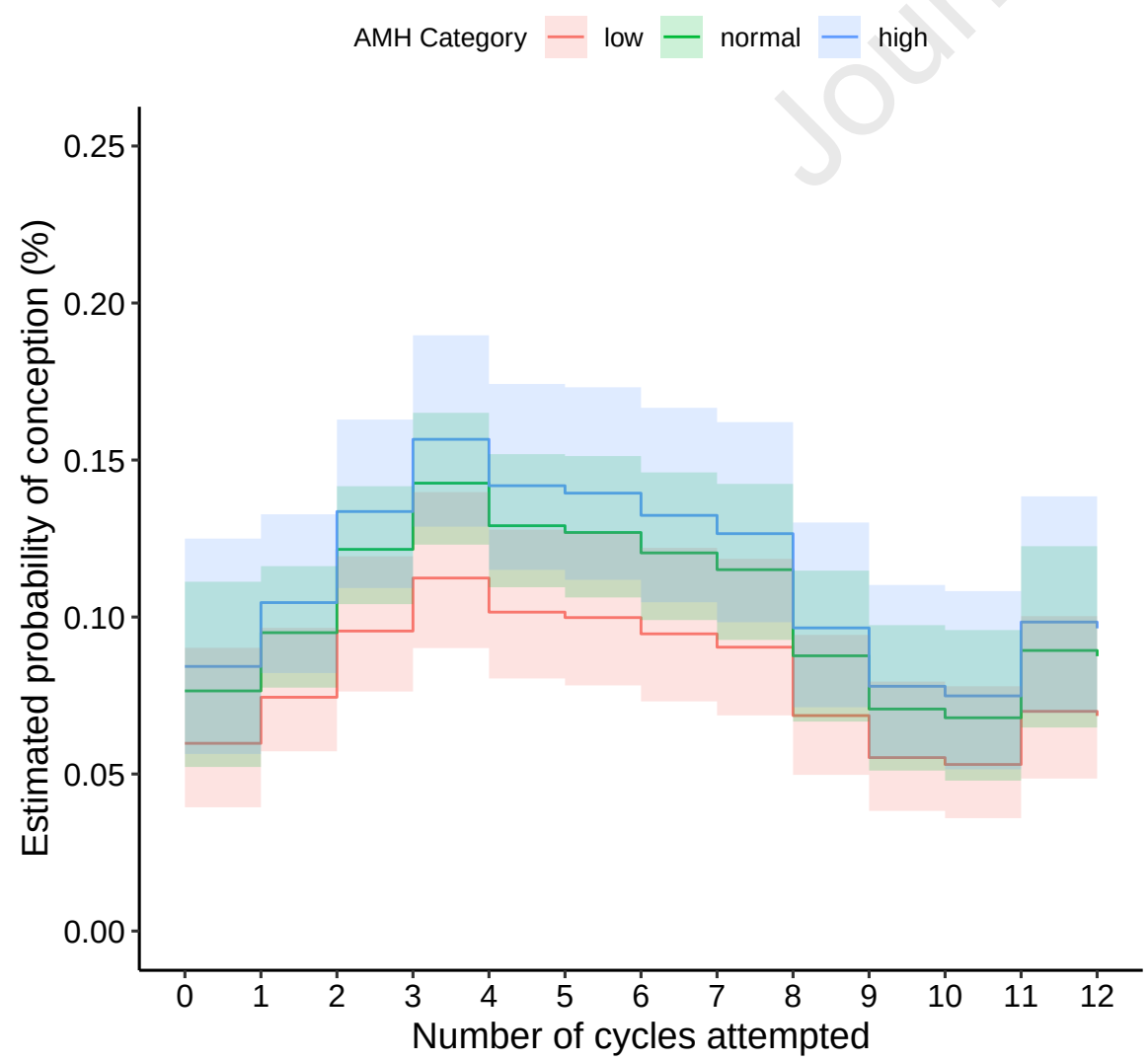

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