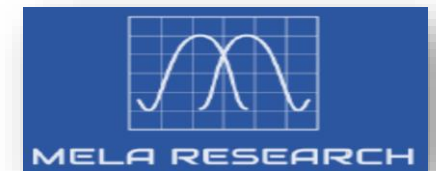


Effect of Enhancing Nutrition, and Antenatal Infection Treatment (ENAT) intervention on birth weight in Ethiopia: A cluster Randomized Controlled Trial



October 2022, Addis Ababa



Outline

- Background, Evaluation hypothesis
- Trial design & methodology
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Background

- Enhancing Nutrition, and Antenatal Infection Treatment (ENAT) intervention was designed to improve newborns birth weight by strengthening the content and quality of ANC.
- ENAT was implemented in 65 health centers in the Amhara and Oromia regions of Ethiopia
- Project duration: *from August 2018 to March 2022, including the preparatory and implementation phases.*
- Implemented by Jhpiego, funded by CIFF and Bill and Melinda Gates Foundation.

Background

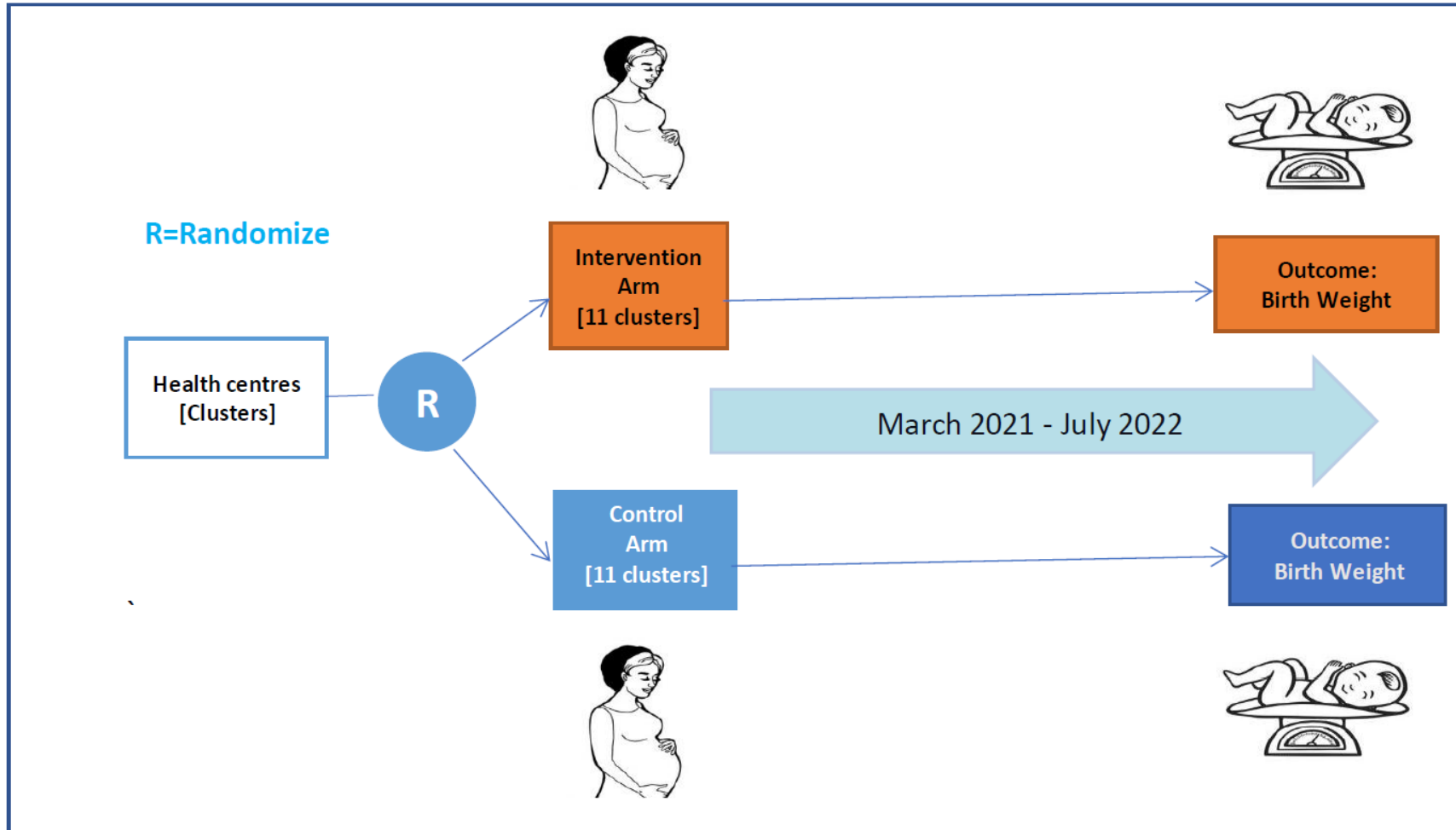
- **ENAT - a bundle of intervention activities ...**
 - strengthening/introducing point of care testing
 - screening for infection and treatment, and provision of preventive care
 - training of health care providers on basic ANC provision including comprehensive counseling
 - introduction of a pregnancy test with the aim of early identification and enrollment of pregnant women
 - strengthen/introduce a system for tracking pregnant women to verify and support continuity of care (adherence to ANC service)

Hypothesis & the ENAT evaluation

- This evaluation tested the hypothesis that the ENAT intervention would increase mean birth weight (primary outcome) by at least 70 grams
- As a secondary outcome, the evaluation also tested whether the ENAT intervention would reduce the incidence of LBW (<2500 grams) by at least 30%
- External evaluation was an integral part of the ENAT intervention, and this activity was tasked to Mela Research, an independent consulting firm.

Trial design & Methods

- ENAT evaluation design: *A two-arm parallel cluster-randomized controlled trial (CRCT)*



Trial design & Methods

- 22 health centers (clusters), randomized equally between 11 intervention (n=4868 pregnant women) and 11 control clusters (n=4821 pregnant women).
- Enrollment into the study took place at the first ANC booking from March 2021 to November 2021 until the trial sample size was achieved.
- The pregnant women were followed until the end of pregnancy or lost to follow-up
- Enrollment & follow-up period: *March 2021- July 2022*

Trial design & Methods

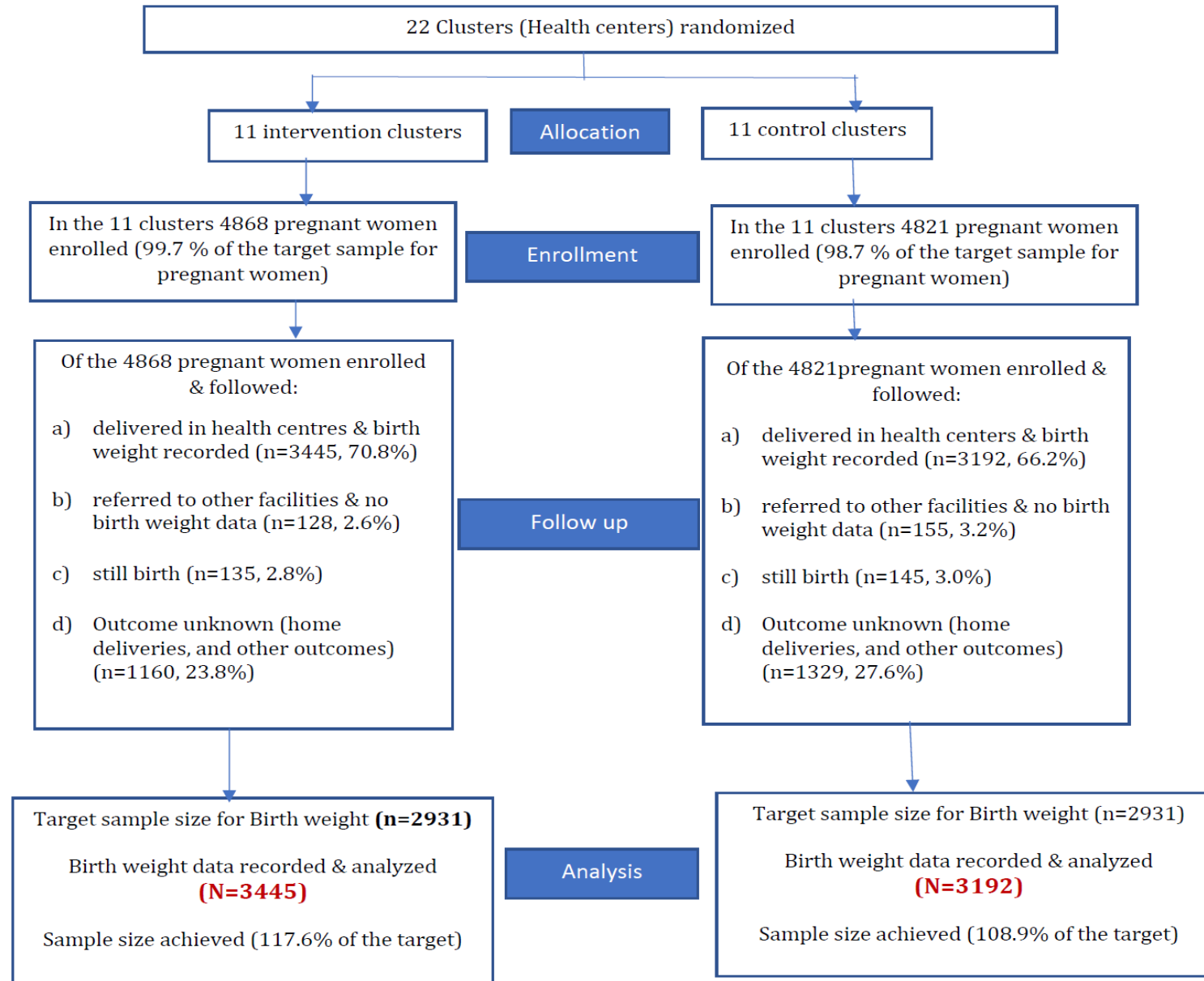
- **Final sample size (with birth weight data):**

- n=3445 (intervention); n=3192 (control)
- More than the anticipated sample size for BW

- **Analysis:**

- Outcomes: ***Mean birth weight (primary) & LBW (secondary)***
- Overall & sub-group analysis (*by sex of the newborn, mother's age & gestational age at first ANC visit*)
- Cluster-weighted chi-square test to compare categorical variables between the two arms & Cluster-adjusted-t-test to compare continuous variables between the two arms
- Multilevel analyses using random effect models to adjust for clustering and selected individual-level covariates.

Participants flow diagram



Enrollment characteristics

- Enrolment characteristics of pregnant compared between the intervention and control arms.
- Assessed for balances or imbalances of CRCT participants at enrolment in terms of selected characteristics
- NO statistically significant differences between the two arms in terms of *participants' age, education, household wealth, the number of pregnancies, number of living children, their birth-to-pregnancy interval, maternal weight, MUAC and the gestational age at first ANC booking.*
- **Interpretation: Similarities of participants between the two arms suggest that the goal of randomization was largely met**



Selected enrollment characteristics

	Intervention		Control		Intervention Vs. Control @
	n	%	n	%	
Women's age					
<20	336	6.9	364	7.6	0.965
20-24	1,498	30.8	1,451	30.1	
25-34	2,566	52.7	2,520	52.3	
35-49	467	9.6	479	9.9	
<i>Mean age (95% CI)</i>	<i>4867</i>	<i>26.0(25.3-26.6)</i>	<i>4814</i>	<i>26.1(25.5-26.8)</i>	<i>0.6030</i>
Education					
No education	2,298	47.2	2,070	42.9	0.7723
grade 1-6	940	19.3	808	16.8	
grade 7-8	696	14.3	656	13.6	
grade 9+	934	19.2	1,287	26.7	
Wealth quintiles					
Lowest	1,198	24.6	742	15.4	0.7551
Second	1,074	22.1	861	17.9	
Middle	832	17.1	1,105	22.9	
Fourth	905	18.6	1,033	21.4	
Highest	858	17.6	1,080	22.4	

Selected enrollment characteristics

	Intervention		Control		Intervention Vs. Control @
Number of pregnancies					
1	1,643	33.8	1,643	34.1	0.5081
2	961	19.7	1,128	23.4	
3	725	14.9	743	15.4	
4 +	1,538	31.6	1,307	27.1	
<i>Mean number of pregnancies (95% CI)</i>	4867	2.8(2.6-3.0)	4821	2.7(2.4-2.9)	0.3795
Birth to pregnancy interval					
<24 months	418	13.4	503	16.8	0.7215
24-35 months	736	23.6	588	19.6	
36-47 months	769	24.7	602	20.1	
48 + months	1,193	38.7	1,299	43.4	
Mid Upper Arm Circumference (MUAC)					
<23 CMS	650	14.0	508	13.0	0.8502
23 CMS or higher	4007	86.0	3405	87.0	
Timing of first ANC visit					
<16 weeks	1807	38.6	1642	34.5	0.4622
16-27 weeks	2187	46.7	2486	52.2	
>27 weeks	692	14.7	632	13.3	

ANC visits

- The pregnant women who participated in the two arms (with BW) initiated first ANC, on average, at around 18 weeks of pregnancy.
- The proportion that started early ANC (i.e., before 16 weeks) was 37.4% in the intervention & 33.3% in the control
- Three-quarter of the pregnant women (with BW) in both arms had attended four or more ANC visits.
- **Interpretation:** No evidence of ENAT improving early ANC booking in the health centers
No evidence of ENAT improving ANC4+ in the health centers

Timing of first visit & number of Visits (among those with BW)

	Intervention		Control	
	N	%	n	%
Timing of first ANC visit				
First ANC visits: <16 weeks	1249	37.4	1054	33.3
First ANC visits: 16-27 weeks	1581	47.3	1692	53.4
First ANC visits: >27 weeks	511	15.3	423	13.3
<i>Timing of first ANC in weeks (Mean & 95% CI)</i>	<i>3341</i>	<i>17.9(17.6-18.2)</i>	<i>3169</i>	<i>18.1(17.8-18.4)</i>
Number of ANC visits				
Number of ANC visits: <4 visits	829	24.1	781	24.5
Number of ANC visits: 4 or more visits	2616	75.9	2411	75.5

ANC services received/provided

- Compared the different services the pregnant women received during ANC between the two arms – (*maternal assessment/testing, preventive interventions, nutrition related services, etc*)
- A summary coverage score created based on 17 ANC services (i.e., *trichotomized coverage score into three: Low, Middle & High*)
- Comparison made.....:
 - *Individual service coverage (%) by arm*
 - *Summary score coverage (%) by arm*

ANC services received/provided

- The ANC services with significantly higher coverage in the intervention arm compared to the control were:
 - *Hemoglobin test*
 - *Screening for asymptomatic bacteriuria (ASB)*
 - *Urinalysis for protein test*
 - *Syphilis test*
 - *Urinalysis for sugary test*
 - *Blood grouping RH*
 - *Deworming tablet given*
 - *MUAC measurement*
 - *Women weight measurement*
 - *Fundal height measurement*
- The summary score (overall coverage indicator) also found significantly higher coverage in the intervention than in the control
- **Interpretation**: The data confirmed that pregnant women attending ANC in the ENAT health centers had much higher access to and coverage of several POC testing and other essential ANC services compared to those in the control.

ANC services received/provided

	Intervention N=3445	Control N=3192	Absolute difference (%) (Intervention-Control)
	%	%	
Basic ANC services (at least once)			
Women weighted	97.8	80.9	+16.9
Fundal height measured	60.8	49.1	+11.7
Blood pressure measured	93.6	92.9	+0.7
Maternal assessment (at least once)			
Hemoglobin test	93.0	56.8	+36.2
Screened for asymptomatic bacteriuria (ASB)	71.2	39.0	+32.2
Urinalysis for protein test	95.6	68.1	+27.5
Syphilis tested	94.3	71.9	+22.4
Urinalysis for sugary test	58.8	42.9	+15.9
Blood grouping RH	90.0	82.0	+8.0
HIV tested	95.8	94.7	+1.1
Hepatitis tested	81.9	84.2	-2.3
Preventive measures (at least once)			
Tetanus Toxoid Injection (TTI) given	98.3	94.1	+4.2
Maternal nutrition assessment & nutrition intervention (at least once)			
Deworming tablet given	49.7	8.1	+41.6
MUAC measurement taken	96.2	82.6	+13.6
Iron folate given	89.2	86.8	+2.4
Summary score (ANC services received)			P-value=0.033 @
Low	13.8	38.7	-24.9
Middle	24.9	43.0	-18.1
High	61.3	18.3	+43.0

@P-value compares summary score between the intervention and control areas, P-value adjusted for clustering

Mean Birth weight (Primary outcome)

- Significantly higher mean birth weight in the intervention (3152 grams) than in the control (3044 grams)
- The mean difference in birth weight between the two arms was 108 grams & is statistically significant
- The subgroup analyses by newborn sex, mother's age and gestational age at the first ANC visit found consistently significantly higher mean birth weight in the intervention arm compared to the control across the different subgroups.
- Multivariate analyses using random effect model that adjusted for clustering & selected covariates further confirmed the univariate findings
- **Interpretation: Babies born to mothers receiving the ENAT intervention were significantly heavier than those babies born to mothers who did not. The mean difference in birth weight recorded by this study of 108 grams is higher than the minimum anticipated effect size of 70 grams for this evaluation.**

Mean Birth Weight by study arm

	Intervention		Control		Absolute difference in mean birth weight (p-value)	95% Confidence Interval	
	n	mean BW(SD)	n	mean BW(SD)		Lower	Upper
All sample	3445	3152.1 (339.8)	3192	3044.1(353.8)	(+)108.0 (p=0.000)	91.3	124.6
Newborn sex							
Male	1773	3168.1(342.9)	1647	3062.1 (352.2)	(+)106.0 (p=0.018)	82.7	129.3
Female	1672	3135.2(335.7)	1545	3025.0(354.5)	(+)110.2 (p=0.014)	86.3	134.0
Age of mother							
15-19	218	3116.8(320.3)	241	3014.4(368.8)	(+)102.4(p=0.027)	38.8	166.1
20-24	1056	3128.4(333.5)	959	3045.3(361.6)	(+)83.1(p=0.047)	52.6	113.4
25-34	1827	3163.1(335.9)	1709	3052.7(340.9)	(+)110.4(p=0.014)	88.0	132.7
35-49	344	3188.0(383.1)	282	3012.0(387.2)	(+)176.0(p=0.008)	116.1	237.6
Gestational age at first ANC visit							
<16 weeks	1249	3136.5(353.4)	1054	3018.3(371.7)	(+)118.2(p=0.017)	88.6	147.9
16+ weeks	2092	3165.0(331.1)	2115	3057.9(341.6)	(+)107.1(p=0.033)	86.8	127.5

Multivariate analysis – adjusted effect of the intervention on Mean Birth Weight

	Model 1 <i>(Adjusted for clustering)</i>		Model 2 <i>(Adjusted for clustering and selected covariates @)</i>	
	β coefficient	P-value	β coefficient	P-value
Study arm				
Control	0.0			
Intervention	122.4	0.006	113.0	0.011
/sigma_u (Between-Cluster variance)	102.4		99.9	
/sigma_e (Within-Custer Variance)	331.7		335.4	
Rho (Intra Class Correlation - ICC)	0.086		0.100	
<i>Adjusted for newborn sex, timing of first ANC visit, women's age, education, wealth, number of pregnancies, birth to pregnancy interval, MUAC, number of ANC visits</i>				

Low Birth Weight (LBW)-secondary outcome

- The incidence of LBW (BW<2500 grams) was significantly lower in the intervention (4.7%) compared to the control (7.3%)
- Compared to the control arms, the incidence of LBW was lower by 35.6% in the intervention arm.
- Sub-group analysis showed consistently lower incidence of LBW in the intervention vs. control across the different subgroups - by sex of the newborn, age of mother & gestational age at first ANC booking
- Multivariate analyses using random effect model that adjusted for clustering & selected covariates further confirmed the univariate findings
- **Interpretation: Babies born to mothers receiving the ENAT intervention were less likely to weight less than 2500 grams (LBW) compared to those babies born to mothers who did not.**

LBW by study arm

	Intervention		Control		P-value	% Difference in LBW <i>[1-(LBWInt/LBWCon)]*100</i>
	n	LBW %	n	LBW%		
All sample	3445	4.7	3192	7.3	0.018	(-) 35.6%
Newborn sex						
Male	1773	4.7	1647	7.0	0.041	(-) 32.8%
Female	1672	4.7	1545	7.6	0.055	(-) 38.1%
Age of mother						
15-19	218	5.5	241	7.9	0.310	(-) 30.4%
20-24	1056	5.2	959	8.4	0.059	(-) 38.1%
25-34	1827	4.2	1709	6.6	0.002	(-) 36.3%
35-49	344	5.2	282	7.1	0.336	(-) 26.8%
Gestational age at first visit						
<16 weeks	1249	5.1	1054	8.7	0.048	(-) 41.4%
16+ weeks	2092	4.3	2115	6.5	0.049	(-) 35.4%

Multivariate analysis – adjusted effect of the intervention on LBW

	Model 1 (Adjusted for clustering)		Model 2 (Adjusted for clustering & selected covariates @)	
	Risk Ratio	P-value	Risk Ratio	P-value
Study arm				
Control	1.0			
Intervention	0.610	0.005	0.645	0.0270
/lnsig2u	-2.039			
Sigma_u (Between-cluster variance)	0.326		0.361	
Rho (Intra Class Correlation - ICC)	0.031		0.038	
<i>Ps: reference category in parenthesis; @ adjusted for newborn sex, first ANC visit, women's age, education, wealth, number of pregnancies, birth to pregnancy interval, MUAC, number of ANC visits</i>				

Lost-to-follow up (LTFU) analysis

- **Los-to-follow up** : No Birth Weight (BW) data due to different reasons
- **Lost –to-follow up occur**
 - if a woman did not come to the facility for a follow-up visit, changed her residence, died.... [NO BW DATA]
 - If baby miscarriages, aborted, stillbirths or died before its weight is taken [NO BW DATA]
 - Home deliveries were also considered lost-to-follow-up. [NO BW DATA]
- **Lost-to-follow up %**
 - 29.2% in the intervention and 33.7% in the control
 - *Sample size requirements for BW assumed up to 40% lost to follow-up due to different reasons, the predominant reason being home deliveries.*

Lost-to-follow up analysis

- Compared selected background characteristics of those lost-to-follow up, and those who are the basis for the final analysis
- No statistically significant differences between those LTFU and those with the outcome in terms of several enrollment characteristics
- **Interpretation**: Those with the outcome and those lost-to-follow-up were broadly similar in terms of several enrolment characteristics, suggesting that the main outcome is unlikely to be biased by the lost-to-follow-up of the participants.

LTFU Vs. those with outcomes

	Intervention			Control		
	Outcome recorded	LTFU	P-value	Outcome recorded	LTFU	P-value
	n=3445	n=1423		n=3192	n=1629	
Women's age			0.8799			0.4074
<20	6.3	8.3		7.6	7.6	
20-24	30.7	31.1		30.1	30.3	
25-34	53.0	52.0		53.6	50.0	
35-49	10.0	8.7		8.8	12.1	
Education			0.9957			0.9983
No education	47.8	45.9		43.5	41.8	
grade 1-6	19.4	19.0		16.9	16.6	
grade 7-8	14.5	13.8		13.4	14.1	
grade 9+	18.3	21.3		26.3	27.6	
Number of pregnancies			0.8269			0.9269
1	32.5	36.8		33.0	36.2	
2	20.4	18.2		24.2	21.9	
3	15.2	14.3		16.0	14.2	
4 +	32.0	30.7		26.8	27.8	
Gestational age at first visit			0.8559			0.799
<16 weeks	37.4	41.5		33.3	37.0	
16-24 weeks	47.3	45.1		53.4	49.9	
>24 weeks	15.3	13.5		13.4	13.1	

LTFU Vs. those with outcomes

	Intervention			Control		
	Outcome recorded	LTFU	P-value	Outcome recorded	LTFU	P-value
	n=3445	n=1423		n=3192	n=1629	
Wealth quintiles			0.9960			0.9997
Lowest	23.4	27.5		15.4	15.3	
Second	23.2	19.3		17.5	18.5	
Middle	17.5	16.0		22.1	24.6	
Fourth	18.5	18.9		21.7	20.9	
Highest	17.3	18.4		23.3	20.8	
Birth to pregnancy (current) interval			0.8525			0.9851
First pregnancy	32.9	37.0		34.2	37.4	
<24 months	9.9	6.2		10.7	11.3	
24-35 months	16.1	14.3		12.8	12.6	
36-47 months	15.9	17.1		13.5	12.1	
48 + months	25.2	25.4		28.9	26.7	

Birth weight data quality assessment

- BW data quality assurance:
 - Initial assessment of facility BW data & key quality issues identified by this evaluation
 - New digital newborn weight scale distributed (*known as Dr. Care*) to the 22 study health centers of both arms.
 - Provided practical in-service training to the facilities midwives/nurses on the new BW scale, calibration and data recording



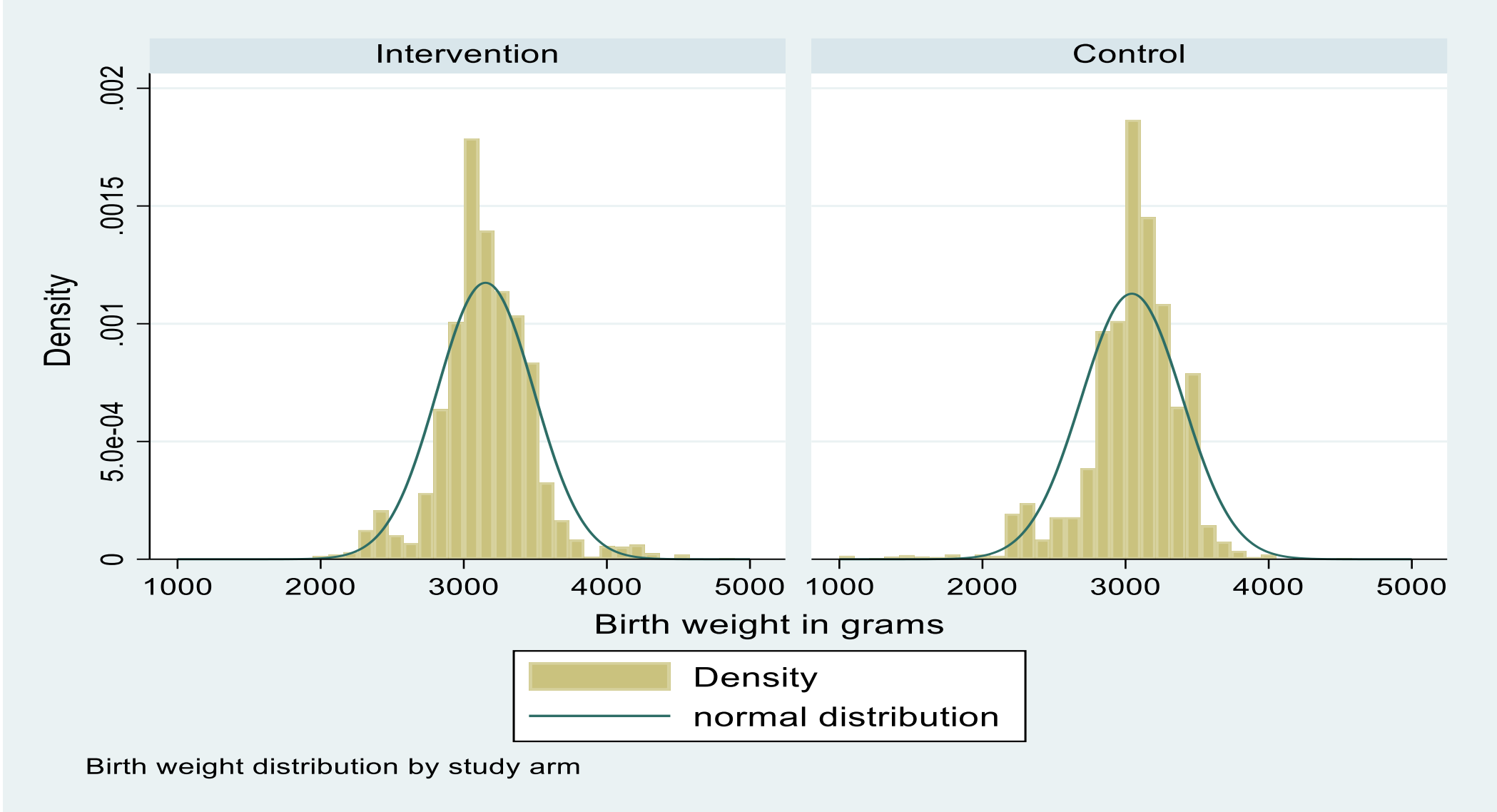
Birth weight data quality assessment

- The overall level of heaping of birth weights at an increment of 500 (i.e., at birth weights of 1500, 2000, 2500, 3000, 3500 grams) was 11.2% & this was lower than over 60% for the EDHS, and other published studies – 41%
- Heaping at 2500 grams was low at 0.78%, compared to 9.6% in the EDHS
- Heaping more common at 3000 grams, but lower than available estimates (5.5% this study & 26.3% EDHS)
- The magnitude of BW heaping did not vary by study arm & clusters
- **Interpretation: Birth weight data of this evaluation is of fairly good quality with heaping occurring at a relatively lower magnitude as compared to the few previously available studies**

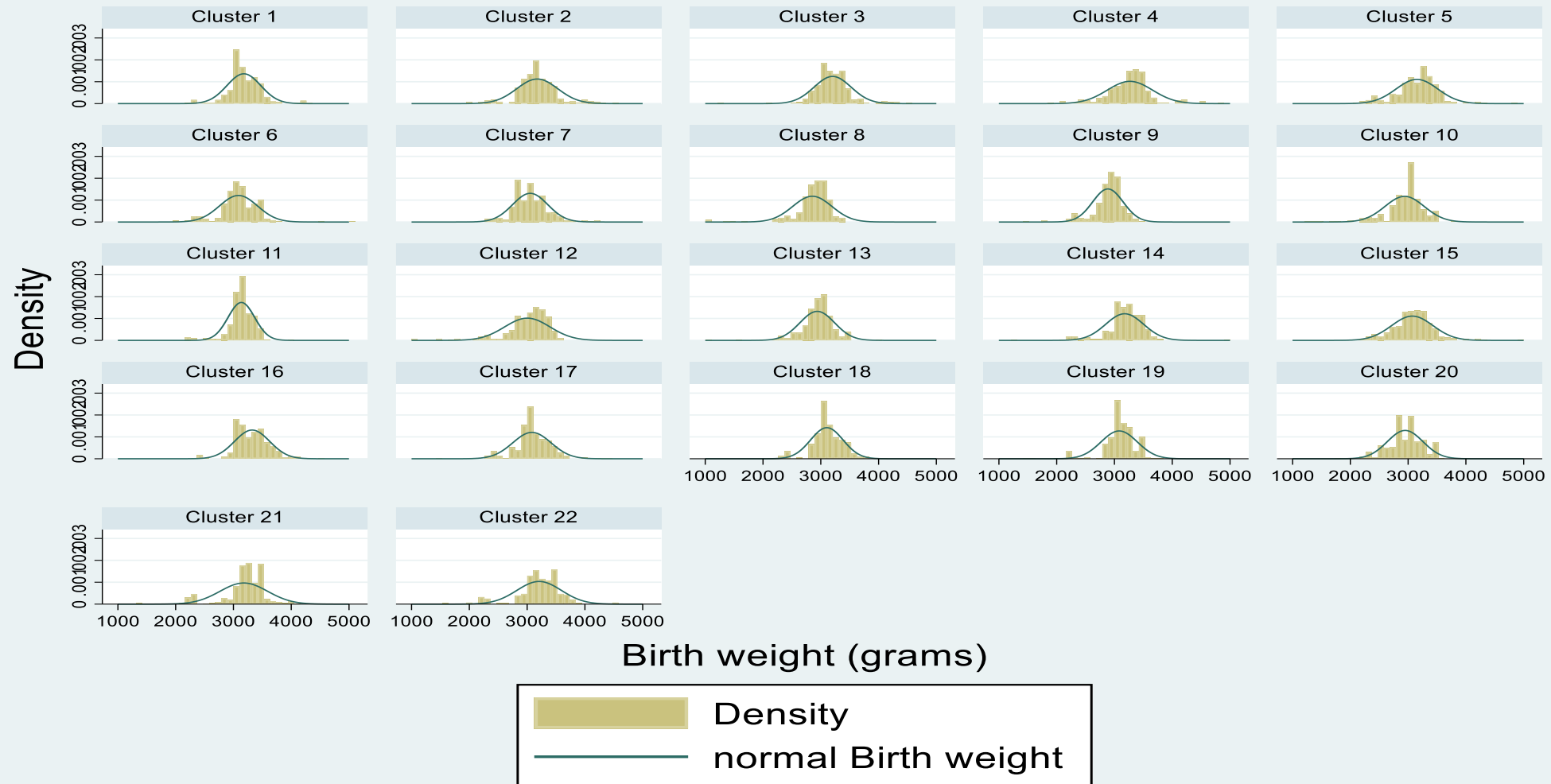
BW heaping at increment of 500 grams

Birth weight recorded	ENAT Evaluation	Birthweight quality improvement (QI) initiative study in Amhara region <i>[Baye et al. Popul. Health Metrics, (2021):19:35]</i>		DHS 2016
		Pre-QI	Post-QI	
[Heaping 500 grams increment]	N=6367	N=1383	N=1371	N=2079
	%	%	%	%
1500	0.11	0.14	0.07	0.67
2000	0.15	0.22	0.80	7.27
2500	0.78	5.42	2.26	9.62
3000	5.51	26.0	6.70	26.3
3500	4.67	9.18	2.19	16.4
Overall heaping by increment of 500	11.2	41.0	12.0	60.3

Birth weight Distribution by study arm



Birth weight Distribution by cluster



Distribution of birth weight by cluster

Strengths of the evaluation

- Use of CRCT
- very large sample size with adequate statistical power
- fairly good BW data quality
- employed rigorous statistical techniques
- the evaluation did not interfere with the day-to-day routine ANC services of the study health centers
- followed standard reporting & analysis format for a CRCT – CONSORT - Consolidation of Standards for Reporting Trials (*Ref: How to design, analyze and report CRCT in Medicine and Health Research Michael J Campbell, Stephen J Walter. ISBN 978-1119-99202-8*)

Limitations of the evaluation

- No similar quality assurance was implemented for the routine ANC data other than BW

(Assumption: any data quality issues of the ANC service data used in this evaluation were not related systematically to the study arms, and thus unlikely to bias the findings.)

- Those LTFU did NOT in general differ from those with outcome on several background characteristics. However, one cannot rule out the presence of unmeasured factors that could vary between those with the outcome and those lost to follow-up

(Assumption: any unmeasured confounder (if any) were not related systematically to the study arms, and thus unlikely to bias the findings.)

Conclusion

- The findings of this evaluation provide sufficient evidence of the effectiveness of the ENAT intervention in improving newborn weight in the study population.
- ENAT is likely to resonate with maternal and newborn health programmers for it has demonstrated that existing routine ANC packages in public facilities can improve birth weight further when implemented fully and appropriately with particular emphasis on point of care testing and infection prevention.
- The cost analysis of ENAT is currently underway and will clarify the additional cost incurred by the intervention.

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- Mr. Solomon Abebe of Jhpiego-Ethiopia
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- Midwives and Nurses in the study health centers
- The pregnant women participated in the study
- Mela evaluation team