MOST Ancillary Study 11-02 (AS11-02)
"Hyperglycemia and Risk of OA" (Ann Schwartz, Nancy Lane)

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1. Dataset description and Analyst Notes

Dataset: AS1102_bioassay.sas7bdat
Observations: 999 records (999 participants, 2 assays; 1 visit)
Documentation:

- VariableGuide_ AS1102_bioassay.pdf
- Distributions_ AS1102_bioassay.pdf

AS1102_bioassay dataset contains 999 records (one record per participant). Two assays were performed at the UC Davis Laboratory on baseline serum samples.

Note: the laboratory performing the assays was blinded to subject ID and clinical characteristics.

The Multicenter Osteoarthritis Study (MOST) collected fasting blood from all study participants at the baseline study visit. This ancillary study, "Hyperglycemia and Risk of OA (AS11-02)", under the direction of Dr. Ann Schwartz and Dr. Nancy Lane, was funded to investigate the relation of serum glucose and insulin content and incidence of radiographic knee OA at any time between baseline and the 84m clinic visit.

Analyst Notes:

- If there was insufficient volume or some other reason assay could not be performed, and all assay values were missing, the record is not included in the analytical dataset.

2. Selection plan

Enrolled in MOST: N=3026 participants / 6052 knees
Use KL grade at baseline visit to classify participants.
Use BL-15-30-60-84m x-ray readings to identify cumulative incidence OA.

Table 1. X-ray reading status among enrolled participants

X-ray readings	No follow up x-ray or medical documentation about KR	No OA (at least one follow up x-ray read)	Incidence OA (BL to 84m)	KR in the no OA knee (BL to 84m)	Incidence RA or necrosis
KL 0 or 1 both knees Both knees eligible for incidence **N=1419**	98	**897**	**385**	**33**	**6**
KL 0 or 1 one knee One knee eligible for incidence **N=711**	-	-	**-**	**-**	-
KL 2 or 3 either knee At least one knee eligible for progression **N=776**	-	-	-	-	-
KL 4 or KR both knees End stage **N=120**	-	-	-	-	-
Total **N=3026**					

Inclusion/Exclusion Criteria:
(1) Include participants with both knees KL grade 0 or 1 at baseline
1419 participants
(2) Include participants with known follow up OA status: no incidence on follow up x-ray, cumulative incidence OA or KR (BL to 84m)
1321 participants

Table 2. Biological specimen status among eligible participants.

Strata	No serum	Serum in storage, but not fasting	Serum in storage and fasting		
KL 0 or 1 both knees Both knees eligible for incidence **N=1321**	35	6	**1280**		

(3) Include participants with serum in storage (presumably) and fasting status=Yes (at least 2 hours fasting self-reported)
1280 participants

Random selection: all 1280 participants are subset by sex: 746 women and 534 men; then divided into 10 groups by gender specific BMI (each group contains approx. 74 women and approx. 53 men).

For the final sample, randomly selected 58 women and 42 men in each BMI decile group. Total sample of 1000 participants selected (see Table 3A and Table 3B for details).

Table 3A. Demographic characteristics in eligible participants (746 women)

WOMEN	BMI groups										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
Women (N participants)	**74**	**74**	**76**	**74**	**75**	**73**	**77**	**74**	**75**	**74**	**746**
BMI range	[16.72 - 22.91]	[22.93 - 24.43]	[24.44 - 25.64]	[25.66 - 26.90]	[26.91 - 28.26]	[28.28 - 29.61]	[29.63 - 31.17]	[31.23 - 32.86]	[32.89 - 35.72]	[35.73 - 50.13]	
Clinic (UAB) N	37	32	37	44	44	27	38	33	32	38	362
%	50	43.24	48.68	59.46	58.67	36.99	49.35	44.59	42.67	51.35	48.53
Race – White N	69	72	71	67	65	61	64	61	66	50	646
%	93.24	97.3	93.42	90.54	86.67	83.56	83.12	82.43	88	67.57	86.6
Bilateral KL=0	59	55	51	57	53	49	57	49	47	38	515
%	79.73	74.32	67.11	77.03	70.67	67.12	74.03	66.22	62.67	51.35	69.03
Bilateral KL 1&0,1&1	15	19	25	17	22	24	20	25	28	36	231
%	20.27	25.68	32.89	22.97	29.33	32.88	25.97	33.78	37.33	48.65	30.97
Outcome											
No OA	63	51	55	52	46	47	53	42	36	35	480
%	85.14	68.92	72.37	70.27	61.33	64.38	68.83	56.76	48	47.3	64.34
Incidence OA	10	19	19	20	28	25	22	30	31	36	240
%	13.51	25.68	25	27.03	37.33	34.25	28.57	40.54	41.33	48.65	32.17
Incidence KR	1	3	2	2	1	1	1	2	7	3	23
%	1.35	4.05	2.63	2.7	1.33	1.37	1.3	2.7	9.33	4.05	3.08
Incidence RA, necrosis	0	1	0	0	0	0	1	0	1	0	3
%	0	1.35	0	0	0	0	1.3	0	1.33	0	0.4
Selected for assay	**58**	**58**	**58**	**58**	**58**	**58**	**58**	**58**	**58**	**58**	**580**
Age- mean (SD)	61.5 (7.9)	61.4 (7.6)	62.2 (8.2)	61.1 (8.3)	63.5 (8.2)	61.4 (7.4)	60.4 (7.4)	59.4 (7.6)	59.1 (6.6)	57.2 (6.7)	**60.7 (7.7)**
Clinic (UAB) N	30	24	28	34	33	21	29	26	27	31	283
%	51.72	41.38	48.28	58.62	56.90	36.21	50.00	44.83	46.55	53.45	48.79
Race – White N	54	56	54	52	50	50	49	47	51	40	503
%	93.10	96.55	93.10	89.66	86.21	86.21	84.48	81.03	87.93	68.97	86.72
Bilateral KL=0	47	44	41	44	41	43	44	39	35	29	407
%	81.03	75.86	70.69	75.86	70.69	74.14	75.86	67.24	60.34	50.00	70.17
Bilateral KL 1&0,1&1	11	14	17	14	17	15	14	19	23	29	173
%	18.97	24.14	29.31	24.14	29.31	25.86	24.14	32.76	39.66	50.00	29.83
Outcome											
No OA	50	40	45	41	35	41	42	32	27	26	379
%	86.21	68.97	77.59	70.69	60.34	70.69	72.41	55.17	46.55	44.83	65.34
Incidence OA	8	14	12	16	22	17	16	25	23	31	184
%	13.79	24.14	20.69	27.59	37.93	29.31	27.59	43.10	39.66	53.45	31.72
Incidence KR	0	3	1	1	1	0	0	1	7	1	15
%	0.00	5.17	1.72	1.72	1.72	0.00	0.00	1.72	12.07	1.72	2.59
Incidence RA, necrosis	0	1	0	0	0	0	0	0	1	0	2
%	0.00	1.72	0.00	0.00	0.00	0.00	0.00	0.00	1.72	0.00	0.34

Table 3B. Demographic characteristics in eligible participants (534 men)

MEN	BMI groups										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
Men (N participants)	**53**	**53**	**54**	**53**	**54**	**53**	**54**	**53**	**54**	**53**	**534**
BMI range	[18.54 - 24.10]	[24.17 - 25.83]	[25.86 - 27.09]	[27.11 - 28.04]	[28.06 - 29.04]	[29.05 - 30.04]	[30.10 - 31.24]	[31.25 - 32.70]	[32.79 - 34.80]	[34.91 - 52.39]	
Clinic (UAB) N	24	19	26	23	35	26	33	25	33	27	271
%	45.28	35.85	48.15	43.4	64.81	49.06	61.11	47.17	61.11	50.94	50.75
Race – White N	46	49	46	48	41	46	40	44	46	46	452
%	86.79	92.45	85.19	90.57	75.93	86.79	74.07	83.02	85.19	86.79	84.6
Bilateral KL=0	40	37	40	37	45	35	38	39	34	28	373
%	75.47	69.81	74.07	69.81	83.33	66.04	70.37	73.58	62.96	52.83	69.9
Bilateral KL 1&0,1&1	13	16	14	16	9	18	16	14	20	25	161
%	24.53	30.19	25.93	30.19	16.67	33.96	29.63	26.42	37.04	47.17	30.15
Outcome											
No OA	45	44	38	40	44	42	39	40	28	29	389
%	84.91	83.02	70.37	75.47	81.48	79.25	72.22	75.47	51.85	54.72	72.85
Incidence OA	8	8	16	11	9	11	15	13	23	19	133
%	15.09	15.09	29.63	20.75	16.67	20.75	27.78	24.53	42.59	35.85	24.91
Incidence KR	0	0	0	2	1	0	0	0	2	4	9
%	0	0	0	3.77	1.85	0	0	0	3.7	7.55	1.69
Incidence RA, necrosis	0	1	0	0	0	0	0	0	1	1	3
%	0	1.89	0	0	0	0	0	0	1.85	1.89	0.56
Selected for assay	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**42**	**420**
Age – mean (SD)	61.1 (8.2)	61.3 (7.4)	61.9 (8.6)	63.0 (9.0)	60.2 (8.3)	58.9 (7.6)	59.6 (8.1)	60.9 (7.7)	59.8 (7.1)	60.6 (7.6)	**60.7 (8.0)**
Clinic (UAB) N	16	12	21	18	29	20	27	20	29	22	214
%	38.10	28.57	50.00	42.86	69.05	47.62	64.29	47.62	69.05	52.38	50.95
Race – White N	37	38	36	39	32	35	31	35	36	36	355
%	88.10	90.48	85.71	92.86	76.19	83.33	73.81	83.33	85.71	85.71	84.52
Bilateral KL=0	30	31	31	29	34	31	29	29	26	23	293
%											
Bilateral KL 1&0,1&1	12	11	11	13	8	11	13	13	16	19	127
%	28.57	26.19	26.19	30.95	19.05	26.19	30.95	30.95	38.10	45.24	30.24
Outcome											
No OA	38	35	31	31	33	34	30	31	21	21	305
%	90.48	83.33	73.81	73.81	78.57	80.95	71.43	73.81	50.00	50.00	72.62
Incidence OA	4	6	11	10	8	8	12	11	19	16	105
%	9.52	14.29	26.19	23.81	19.05	19.05	28.57	26.19	45.24	38.10	25.00
Incidence KR	0	0	0	1	1	0	0	0	1	4	7
%	0.00	0.00	0.00	2.38	2.38	0.00	0.00	0.00	2.38	9.52	1.67
Incidence RA, necrosis	0	1	0	0	0	0	0	0	1	1	3
%	0.00	2.38	0.00	0.00	0.00	0.00	0.00	0.00	2.38	2.38	0.71

3. Research questions and hypothesis.

Note: research questions and hypothesis extracted from the original ancillary study proposal

1. To determine whether fasting glucose, fasting insulin, or insulin resistance (as measured by the "homeostasis model of assessment - insulin resistance" or "HOMA-IR") is associated with development of radiographic knee osteoarthritis (RKOA), independent of body size, in those with and without diabetes. In addition, we plan to look at individual radiographic features, including joint space narrowing and osteophyte formation, to better characterize this association.

2. To determine whether diabetes at baseline is associated with development of knee OA, independent of body size.

To achieve these aims, we measured fasting glucose and fasting insulin in baseline specimens from 1000 participants without prevalent knee OA at baseline.

Sample of participants for assays

We will include in these analyses a stratified random sample of 1000 subjects enrolled in MOST with: no knee OA at baseline (KL 0 or 1 in both knees), follow up x-rays and/or documentation of progression of knee osteoarthritis, and fasting baseline serum available. The sampling will be stratified on deciles of BMI (i.e. 100 participants will be randomly selected from each decile of BMI). We considered a case-cohort design because we can only cover assay costs for 1,000 participants. However, after consultation with Dr. McCulloch we chose this design using a stratified random sample of the baseline participants. The outcome of incident OA is sufficiently common that we will have adequate case numbers using this approach, and the analysis will be more straightforward. With 1,000 participants, we estimate that 33% (N=330) will develop OA during MOST follow-up. We could not include all eligible participants without OA at baseline (N=1280) because of our budget constraints. We stratified on BMI because control for this variable is essential to determine if diabetes is associated with OA, *independent* of BMI.

4. Preliminary analysis

Identification of diabetes using fasting glucose (FG)

In the sample of 1,000 participants without knee OA at baseline, there were 88 (8.8%) participants identified as diabetic using self-report of diabetes diagnosis and self-report medication use. Fasting glucose assays identified an additional 19 (1.9%) participants with diabetes. An increase of 22% in the number identified as diabetic.

Table 4. Table of characteristics by inclusion/exclusion and missing data (N=1419)

	0: Included in analysis (N=1000)	**1: Eligible for inclusion (N=280)**	**2: Not included – no follow up x-ray or documentation about knee replacement OR no serum in storage OR serum in storage but not fasting (N=139)**	**p-value (**chi-sq for categorical and ANOVA for continuous)
Age mean[median] (SD)	60.7[60.0](7.8)	61.3[61.0](8.1)	60.7[58.0](8.4)	0.4885
Gender (% Female)	580 (58.0%)	166 (59.3%)	81 (58.3%)	0.9283
Race (% White)	858 (85.8%)	240 (85.7%)	116 (83.5%)	0.7592
(% Black)				
Other				
Clinic site (% UAB)	495 (49.5%)	138 (49.3%)	67 (48.2%)	0.9595
BMI mean [median] (SD)	29.1[28.6](4.9)	29.2[28.7](4.8)	29.9[29.7](5.6)	0.1628
Self-Reported Diabetes (including SAQ question and medication inventory)	88 (8.8%)	26 (9.3%)	13 (9.4%)	0.9541
Diabetes=Yes (SAQ question)	86 (8.6%)	26 (9.3%)	13 (9.4%)	0.498
Diabetes medications (any diabetes medications in inventory)	69 (6.9%)	16 (5.7%)	10 (7.2%)	0.7581
Self-Reported Diabetes (combined plus Glucose=126+)	107 (10.7%)	26 (9.3%)	13 (9.4%)	0.7333
Detailed diabetes report				
Glucose=126+ only	19 (1.9%)	-	-	
Medication only	2 (0.2%)	0 (0.0%)	0 (0.0%)	
SAQ=yes only	15 (1.5%)	10 (3.6%)	3 (2.2%)	
SAQ=Yes and Glucose=126+	4 (0.4%)	-	-	
SAQ=Yes and medication	27 (2.7%)	16 (5.7%)	10 (7.2%)	
SAQ=Yes; medications and Glucose=126+	40 (4.0%)	-	-	
Detailed Outcome = no OA	684 (68.4%)	185 (66.1%)	28 (20.1%)	
Outcome missing	-	-	98 (70.5%)	
Outcome=Incidence (at least one knee)	316 (31.6%)	95 (33.9%)	13 (9.4%)	

5. Reference

Rogers-Soeder TS, Lane NE, Walimbe M, Schwartz AV, Tolstykh I, Felson DT, Lewis CE, Segal NA, Nevitt MC; Multicenter Osteoarthritis (MOST) Study Group.
Association of diabetes mellitus and biomarkers of abnormal glucose metabolism with incident radiographic knee osteoarthritis.
Arthritis Care Res (Hoboken). 2020 Jan;72(1):98-106. doi: 10.1002/acr.23809.
PMCID: 6511494
https://www.ncbi.nlm.nih.gov/pubmed/30418707

6. Appendix A. QA analysis of assays results

Coordinating Center performed QA report by assay.

Analyte=Glucose Normal range min=90 Normal range max=110											
Sex	**N obs**	**Mean**	**Median**	**Min**	**Max**	**N within Normal range**	**% within Normal range**	**N below normal**	**% below normal**	**N above normal**	**% above normal**
Female	580	97.21	93	74	345	339	58.45%	181	**31.21%**	60	10.34%
Male	419	104.66	99	68	319	274	65.39%	60	**14.32%**	85	**20.29%**
Glucose	999	100.34	95	68	345	613	61.36%	241	24.12%	145	14.51%

Analyte=Insulin_muU_ml Normal range min=2.6 Normal range max=24.9											
Sex	**N obs**	**Mean**	**Median**	**Min**	**Max**	**N within Normal range**	**% within Normal range**	**N below normal**	**% below normal**	**N above normal**	**% above normal**
Female	579	8.79	6.952	0.201	49.542	499	86.18%	61	**10.54%**	19	3.28%
Male	419	10.71	8.206	0.156	99.914	351	83.77%	43	**10.26%**	25	5.97%
Insulin_muU_ml	998	9.59	7.482	0.156	99.914	850	85.17%	104	10.42%	44	4.41%