Dataset Integrity Check for Bone Density in Children With Chronic Liver Disease Correlates With Growth and Cholestasis – Loomes et al

Prepared by Jane Rideau Demuth
IMS Inc.
3901 Calverton Blvd, Suite 200 Calverton, MD 20705
March 27, 2019

Contents

1 Standard Disclaimer

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is not to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

2 Study Background

The Childhood Liver Disease Research Network (ChiLDReN) is a National Institutes of Health–funded consortium of pediatric centers in North America focused on the study of rare pediatric liver diseases. The Longitudinal Study of Genetic Causes of Intrahepatic Cholestasis (LOGIC; NCT00571272) enrolled children with one of four diagnoses: ALGS, PFIC, A1AT, or bile acid synthetic disorder (BASD). As part of the LOGIC study protocol, participants aged >5 years underwent DXA scanning, the results of which are reported here. The objectives of this study were to address an important knowledge gap by investigating the prevalence of bone mineral deficits in this cohort of children with chronic liver disease and to determine factors associated with lower bone density, including growth parameters, laboratory values, and clinical events such as fracture and biliary diversion.

3 Archived Datasets

All the SAS data files, as provided by the Data Coordinating Center (DCC), are located in the LOGIC folder in the data package. For this replication, variables were taken from the “Loomes_DXA/dxadata.sas7bdat” dataset.

4 Statistical Methods

Analyses were performed to duplicate results for the data published by Loomes et al [1] in the journal Hepatology in 2019. To verify the integrity of the dataset, descriptive statistics were computed.

5 Results

For Table 1 in the publication [1], Demographic and Clinical Characteristics of Participant Population by Disease Group, Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data files to the results published in Table 1.

6 Conclusions

The NIDDK repository is confident that the Loomes_DXA data file to be distributed is a true copy of the study data.

7 References

[1] Loomes K, Spino C, Goodrich N, et al. Bone Density in Children With Chronic Liver Disease Correlates With Growth and Cholestasis**.** *Hepatology* volume 69, issue 1, pages 245-257 (Jan 2019).

Table A: Variables used to replicate Table 1: Demographic and Clinical Characteristics of Participant Population by Disease Group

Table Variable	**dataset.variable**
Liver Disease	dxadata.diagnosis
Male sex	dxadata.sex
Race	dxadata.race
Ethnicity	dxadata.ethnicity
Any bone fractures	dxadata.BoneFractureAny
Frequency of bone fractures	dxadata.BoneFractureNum
Spleen size >2 cm and platelet count <150 x 10^3/ul	dxadata.SpleenPlate
BMI Z score <-2	dxadata.BMIltneg2
Age (years)	dxadata.AgeAtScanYears
Weight Z score	dxadata.WeightZScore
Height Z score	dxadata.HeightZScore
BMI Z score	dxadata.BMIZScore
Lean body mass (%)	dxadata.MeasuredPctLean
TB, mg/dL	dxadata.BiliTotal
Direct bilirubin, mg/dL	dxadata.BiliDirect
GGT, U/L	dxadata.GGT
Alkaline phosphatase, U/L	dxadata.AlkPhos
ALT, U/L	dxadata.ALT
AST, U/L	dxadata.AST
Serum bile acids (µmol/L)	dxadata.CentralBileAcid
OH vitamin D level (ng/mL)	dxadata.VitaminD
INR	dxadata.INR
Albumin, g/dL	dxadata.Albumin
WBC, x10^3/µL	dxadata.WBC
Hemoglobin, g/dL	dxadata.HgB

Table Variable	dataset.variable
Platelet count, $x10^3/\mu L$	dxadata.Plate

Table B: Comparison of values computed in integrity check to reference article Table 1 values

Liver Disease	Variable	MS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	IMS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	Difference
ALGS	n	49	49	0
	Male sex	28 (57%)	28 (57%)	0 (0)
	Race – white	38 (78%)	38 (78%)	0 (0)
	Race – black	5 (10%)	5 (10%)	0 (0)
	Race – other	6 (12%)	6 (12%)	0 (0)
	Ethnicity – Hispanic	4 (8%)	4 (8%)	0 (0)
	Ethnicity – Non-Hispanic	44 (90%)	44 (90%)	0 (0)
	Ethnicity – Not reported	1 (2%)	1 (2%)	0 (0)
	Any bone fractures – No	30 (61%)	30 (61%)	0 (0)
	Any bone fractures – Yes	19 (39%)	19 (39%)	0 (0)
	Frequency of bone fractures – 0/1	40 (82%)	40 (82%)	0 (0)
	Frequency of bone fractures – 2+	9 (18%)	9 (18%)	0 (0)
	Spleen size >2cm and platelet count $<150x10^3/\mu L$	6 (16%)	6 (16%)	0 (0)
	BMI Z Score <-2	3 (6%)	3 (6%)	0 (0)
	Age (years)	10.8 (4.6) 9.8 (7.7, 13.1)	10.8 (4.6) 9.8 (7.7, 13.1)	0 (0) 0 (0, 0)
	Weight Z score	–1.3 (1.3) –1.1 (–2.3, –0.4)	–1.3 (1.3) –1.1 (–2.3, –0.4)	0 (0) 0 (0, 0)
	Height Z score	–1.5 (1.1) –1.6 (–2.1, –0.7)	–1.5 (1.1) –1.6 (–2.2, –0.7)	0 (0) 0 (0.1, 0)
	BMI Z score	–0.6 (1.2) –0.3 (–1.3, 0.3)	–0.5 (1.2) –0.3 (–1.2, 0.3)	0.1 (0) 0 (0.1, 0)
	Lean body mass (%)	73.8 (5.6)	73.8 (5.6)	0 (0)
	TB, mg/dL	3.7 (5.1)	3.6 (5.1)	0.1 (0)
	Direct bilirubin, mg/dL	2.4 (3.2)	2.4 (3.2)	0 (0)

Liver Disease	Variable	MS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	IMS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	Difference
	GGT, U/L	353.6 (309.4)	353.6 (309.4)	0 (0)
	Alkaline phosphatase, U/L	501.9 (345.1)	501.9 (345.1)	0 (0)
	ALT, U/L	164.9 (120.4)	164.9 (120.4)	0 (0)
	AST, U/L	151.8 (110.8)	151.8 (110.8)	0 (0)
	Serum bile acids (µmol/L)	117.3 (106.3)	117.3 (106.3)	0 (0)
	OH vitamin D level (ng/mL)	34.1 (19.0)	34.1 (19.0)	0 (0)
	INR	1.08 (0.16)	1.07 (0.16)	0.01 (0)
	Albumin, g/dL	4.2 (0.6)	4.2 (0.6)	0 (0)
	WBC, $x10^3/\mu L$	6.5 (2.8)	6.5 (2.8)	0 (0)
	Hemoglobin, g/dL	12.9 (1.7)	12.9 (1.7)	0 (0)
	Platelet count, $x10^3/\mu L$	232.5 (105.0)	232.5 (105.0)	0 (0)
CIC	n	41	41	0
	Male sex	18 (44%)	18 (44%)	0 (0)
	Race – white	34 (83%)	34 (83%)	0 (0)
	Race – black	2 (5%)	2 (5%)	0 (0)
	Race – other	5 (12%)	5 (12%)	0 (0)
	Ethnicity – Hispanic	7 (17%)	7 (17%)	0 (0)
	Ethnicity – Non-Hispanic	33 (80%)	33 (80%)	0 (0)
	Ethnicity – Not reported	1 (2%)	1 (2%)	0 (0)
	Any bone fractures – No	31 (76%)	31 (76%)	0 (0)
	Any bone fractures – Yes	10 (24%)	10 (24%)	0 (0)
	Frequency of bone fractures – 0/1	38 (93%)	38 (93%)	0 (0)
	Frequency of bone fractures – 2+	3 (7%)	3 (7%)	0 (0)
	Spleen size >2cm and platelet count $<150x10^3/\mu L$	4 (13%)	4 (13%)	0 (0)
	BMI Z Score <-2	2 (5%)	2 (5%)	0 (0)
	Age (years)	11.0 (5.0) 10.9 (6.6, 15.0)	11.0 (5.0) 10.9 (6.6, 15.0)	0 (0)

Liver Disease	Variable	MS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	IMS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	Difference
	Weight Z score	–1.1 (1.5) –1.1 (–2.0, 0.0)	–1.1 (1.5) –1.1 (–2.0, 0.0)	0 (0, 0)
	Height Z score	–1.3 (1.8) –1.2 (–2.3, –0.3)	–1.3 (1.8) –1.2 (–2.3, –0.3)	0 (0)
	BMI Z score	–0.2 (1.0) –0.1 (–0.8, 0.4)	–0.2 (1.0) –0.1 (–0.8, 0.4)	0 (0, 0)
	Lean body mass (%)	76.4 (7.4)	76.4 (7.4)	0 (0)
	TB, mg/dL	1.6 (1.9)	1.5 (1.9)	0.1 (0)
	Direct bilirubin, mg/dL	0.5 (0.9)	0.5 (0.9)	0 (0)
	GGT, U/L	97.9 (172.5)	97.9 (172.5)	0 (0)
	Alkaline phosphatase, U/L	457.0 (229.8)	457.0 (229.8)	0 (0)
	ALT, U/L	76.2 (53.8)	76.2 (53.8)	0 (0)
	AST, U/L	78.5 (51.5)	78.5 (51.5)	0 (0)
	Serum bile acids (µmol/L)	69.8 (102.2)	69.8 (102.2)	0 (0)
	OH vitamin D level (ng/mL)	37.8 (16.4)	37.8 (16.4)	0 (0)
	INR	1.07 (0.17)	1.07 (0.16)	0 (0.01)
	Albumin, g/dL	4.2 (0.5)	4.2 (0.5)	0 (0)
	WBC, $x10^3/\mu L$	5.9 (2.2)	5.9 (2.2)	0 (0)
	Hemoglobin, g/dL	13.0 (1.4)	13.0 (1.4)	0 (0)
	Platelet count, $x10^3/\mu L$	272.7 (142.2)	272.7 (142.2)	0 (0)
A1AT Deficiency	n	44	44	0
	Male sex	31 (70%)	31 (70%)	0 (0)
	Race – white	43 (98%)	43 (98%)	0 (0)
	Race – black	0 (0%)	0 (0%)	0 (0)
	Race – other	1 (2%)	1 (2%)	0 (0)
	Ethnicity – Hispanic	3 (7%)	3 (7%)	0 (0)
	Ethnicity – Non-Hispanic	40 (91%)	40 (91%)	0 (0)
	Ethnicity – Not reported	1 (2%)	1 (2%)	0 (0)

Liver Disease	Variable	MS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	IMS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	Difference
	Any bone fractures – No	35 (80%)	35 (80%)	0 (0)
	Any bone fractures – Yes	9 (20%)	9 (20%)	0 (0)
	Frequency of bone fractures – 0/1	43 (98%)	43 (98%)	0 (0)
	Frequency of bone fractures – 2+	1 (2%)	1 (2%)	0 (0)
	Spleen size >2cm and platelet count <150x10^3/µL	5 (12%)	5 (12%)	0 (0)
	BMI Z Score <-2	1 (2%)	1 (2%)	0 (0)
	Age (years)	11.0 (5.3) 8.7 (6.5, 14.5)	11.0 (5.3) 8.7 (6.5, 14.5)	0 (0) 0 (0, 0)
	Weight Z score	0.6 (0.9) 0.7 (0.1, 1.2)	0.5 (0.9) 0.6 (0.1, 1.1)	0.1 (0) 0.1 (0, 0.1)
	Height Z score	0.5 (1.2) 0.5 (–0.1, 1.1)	0.5 (1.2) 0.5 (–0.0, 1.1)	0 (0) 0 (0.1, 0)
	BMI Z score	0.4 (1.0) 0.6 (–0.2, 0.9)	0.4 (1.0) 0.6 (–0.2, 0.9)	0 (0) 0 (0, 0)
	Lean body mass (%)	75.8 (7.7)	75.8 (7.7)	0 (0)
	TB, mg/dL	0.8 (1.2)	0.8 (1.2)	0 (0)
	Direct bilirubin, mg/dL	0.1 (0.1)	0.1 (0.1)	0 (0)
	GGT, U/L	57.0 (66.9)	57.0 (66.9)	0 (0)
	Alkaline phosphatase, U/L	234.9 (114.4)	234.9 (114.4)	0 (0)
	ALT, U/L	59.0 (39.2)	59.0 (39.2)	0 (0)
	AST, U/L	61.1 (48.6)	61.1 (48.6)	0 (0)
	Serum bile acids (µmol/L)	16.6 (19.0)	16.6 (19.0)	0 (0)
	OH vitamin D level (ng/mL)	37.8 (10.6)	37.8 (10.6)	0 (0)
	INR	1.06 (0.10)	1.06 (0.10)	0 (0)
	Albumin, g/dL	4.5 (0.4)	4.5 (0.4)	0 (0)
	WBC, x10^3/µL	5.9 (2.5)	5.9 (2.5)	0 (0)
	Hemoglobin, g/dL	13.8 (1.1)	13.8 (1.1)	0 (0)
	Platelet count, x10^3/µL	232.1 (114.8)	232.1 (114.8)	0 (0)

Liver Disease	Variable	MS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	IMS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	Difference
BASD	n	14	14	0
	Male sex	11 (79%)	11 (79%)	0 (0)
	Race – white	11 (79%)	11 (79%)	0 (0)
	Race – black	1 (7%)	1 (7%)	0 (0)
	Race – other	2 (14%)	2 (14%)	0 (0)
	Ethnicity – Hispanic	3 (21%)	3 (21%)	0 (0)
	Ethnicity – Non-Hispanic	11 (79%)	11 (79%)	0 (0)
	Ethnicity – Not reported	0 (0%)	0 (0%)	0 (0)
	Any bone fractures – No	11 (79%)	11 (79%)	0 (0)
	Any bone fractures – Yes	3 (21%)	3 (21%)	0 (0)
	Frequency of bone fractures – 0/1	13 (93%)	13 (93%)	0 (0)
	Frequency of bone fractures – 2+	1 (7%)	1 (7%)	0 (0)
	Spleen size >2cm and platelet count $<150x10^3/\mu L$	0 (0%)	0 (0%)	0 (0)
	BMI Z Score <-2	1 (7%)	1 (7%)	0 (0)
	Age (years)	12.0 (6.7) 8.4 (6.8, 20.0)	12.0 (6.7) 8.4 (6.8, 20.0)	0 (0) 0 (0, 0)
	Weight Z score	0.9 (1.4) 1.1 (–0.2, 1.7)	0.9 (1.4) 1.1 (–0.2, 1.7)	0 (0) 0 (0, 0)
	Height Z score	–0.1 (0.7) 0.1 (–0.5, 0.2)	–0.1 (0.7) 0.1 (–0.5, 0.2)	0 (0) 0 (0, 0)
	BMI Z score	1.0 (1.4) 1.3 (0.4, 1.9)	1.0 (1.4) 1.3 (0.4, 1.9)	0 (0) 0 (0, 0)
	Lean body mass (%)	74.6 (8.5)	74.6 (8.5)	0 (0)
	TB, mg/dL	0.3 (0.3)	0.3 (0.3)	0 (0)
	Direct bilirubin, mg/dL	—	—	—
	GGT, U/L	23.6 (4.9)	23.6 (4.9)	0 (0)
	Alkaline phosphatase, U/L	215.6 (122.7)	215.6 (122.7)	0 (0)
	ALT, U/L	26.1 (22.4)	26.1 (22.4)	0 (0)

Liver Disease	Variable	MS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	IMS n (%) / Mean (SD, Q1, Q3) / Mean (SD)	Difference
	AST, U/L	51.8 (17.0)	51.8 (17.0)	0 (0)
	Serum bile acids (µmol/L)	27.5 (43.4)	27.5 (43.4)	0 (0)
	OH vitamin D level (ng/mL)	25.9 (9.9)	25.9 (9.9)	0 (0)
	INR	1.03 (0.10)	1.02 (0.10)	0.01 (0)
	Albumin, g/dL	4.6 (0.4)	4.6 (0.4)	0 (0)
	WBC, $x10^3$/µL	6.8 (2.2)	6.8 (2.2)	0 (0)
	Hemoglobin, g/dL	14.4 (1.3)	14.4 (1.3)	0 (0)
	Platelet count, $x10^3$/µL	249.1 (109.4)	249.1 (109.4)	0 (0)

Attachment A: SAS Code

```
options mprint nocentre linesize=147 validvarname=upcase;

title "Program:  /prj/niddk/ims_analysis/LOGIC/prog_initial_analysis/DSIC.review.LOGIC-Loomes_DXA.y2019m03d25.sas";
title2 "This program reviews the LOGIC/Loomes_DXA data.";

/*********************************************************************

programmer:  Jane Rideau Demuth

platform:  LINUX SASv9.4

date:  25th March 2019

purpose:  See title2.

*********************************************************************/

***************;
*** formats ***;
***************;
proc format;
  value nmsgf
    . = ' '
    low-high = '###'
    ;
  value $cmsgf
    ' ' = ' '
    other = '$$$'
    ;
  value posnegf
    . = ' '
    low-<0 = '---'
    0 = '0'
    0<-high = '+++'
    ;
  value dxf
    1 = '4-BASD'
    2 = '2-CIC'
    3 = '3-A1AT'
    4 = '1-ALGS'
    ;
  value sexf
    1 = 'Male'
    2 = 'Female'
    ;
  value racef
```

```
    1 = 'White'
    2 = 'Black'
    3-7 = 'Other'
    ;
  value ethnicityf
    1 = 'Hispanic'
    0 = 'Non Hispanic'
    99 = 'Not reported'
    ;
  value yesnof
    0 = 'no'
    1 = 'YES'
    ;
  value bonefracnumf
    0-1 = '0-1'
    2-7 = '2+'
    ;

******************;
*** input files ***;
******************;
libname pcsasin "/prj/niddk/ims_analysis/LOGIC/private_orig_data/Loomes_DXA/DataAndFiles/";
data dxadata;
  set pcsasin.dxadata;
  format _all_;
  informat _all_;

***********************;
*** review the data ***;
***********************;
title3 "Input file:  /prj/niddk/ims_analysis/LOGIC/private_orig_data/Loomes_DXA/DataAndFiles/dxadata.sas7bdat";
proc contents data=dxadata varnum;

************************;
*** replicate table 1 ***;
************************;
proc sort data=dxadata out=dxa;
  where nodxa = 0;
  by diagnosis;

proc freq data=dxa order=formatted;
  title3 'Replicate Table 1';
  tables diagnosis (sex race ethnicity bonefractureany bonefracturenum spleenplate bmiltneg2)*diagnosis / missprint norow nocum;
  format sex sexf.
         race racef.
         ethnicity ethnicityf.
         bonefractureany spleenplate bmiltneg2 yesnof.
         bonefracturenum bonefracnumf.
         diagnosis dxf.;

proc univariate data=dxa noprint;
```

```
  by diagnosis;
  var ageatscanyears weightzscore heightzscore bmizscore;
  output out=dxauni1
         mean=age_mean wtz_mean htz_mean bmiz_mean
         std=age_std wtz_std htz_std bmiz_std
         median=age_mdn wtz_mdn htz_mdn bmiz_mdn
         q1=age_q1 wtz_q1 htz_q1 bmiz_q1
         q3=age_q3 wtz_q3 htz_q3 bmiz_q3;

proc sql;
  create table dxauni1srt as
  select *
  from dxauni1
  order by put(diagnosis,dxf.);

proc print data=dxauni1srt noobs;
  title4 'Age (years)';
  var diagnosis age_mean age_std age_mdn age_q1 age_q3;
  format _numeric_ 4.1
         diagnosis dxf.;

proc print data=dxauni1srt noobs;
  title4 'Weight Z score';
  var diagnosis wtz_mean wtz_std wtz_mdn wtz_q1 wtz_q3;
  format _numeric_ 4.1
         diagnosis dxf.;

proc print data=dxauni1srt noobs;
  title4 'Height Z score';
  var diagnosis htz_mean htz_std htz_mdn htz_q1 htz_q3;
  format _numeric_ 4.1
         diagnosis dxf.;

proc print data=dxauni1srt noobs;
  title4 'BMI Z score';
  var diagnosis bmiz_mean bmiz_std bmiz_mdn bmiz_q1 bmiz_q3;
  format _numeric_ 4.1
         diagnosis dxf.;

proc univariate data=dxa noprint;
  by diagnosis;
  var measuredpctlean bilitotal bilidirect ggt alkphos alt ast centralbileacid vitamind inr albumin wbc hgb plate;
  output out=dxauni2
         mean=leanpct_mean tb_mean dirbili_mean ggt_mean alkphos_mean alt_mean ast_mean
              serumbile_mean vitd_mean inr_mean alb_mean wbc_mean hgb_mean platelet_mean
         std=leanpct_std tb_std dirbili_std ggt_std alkphos_std alt_std ast_std
             serumbile_std vitd_std inr_std alb_std wbc_std hgb_std platelet_std;

proc sql;
  create table dxauni2srt as
  select *
```

```
  from dxauni2
  order by put(diagnosis,dxf.);

proc print data=dxauni2srt noobs;
  title4 'Lean body mass (%), TB, Direct bilirubin, GGT';
  var diagnosis leanpct_mean leanpct_std tb_mean tb_std dirbili_mean dirbili_std ggt_mean ggt_std;
  format _numeric_ 5.1
         diagnosis dxf.;

proc print data=dxauni2srt noobs;
  title4 'AlkPhos, ALT, AST, Serum bile acids, Vit D';
  var diagnosis alkphos_mean alkphos_std alt_mean alt_std ast_mean ast_std serumbile_mean serumbile_std vitd_mean vitd_std;
  format _numeric_ 5.1
         diagnosis dxf.;

proc print data=dxauni2srt noobs;
  title4 'INR, Albumin, WBC, Hemoglobin, Platelet count';
  var diagnosis inr_mean inr_std alb_mean alb_std wbc_mean wbc_std hgb_mean hgb_std platelet_mean platelet_std;
  format _numeric_ 6.2
         diagnosis dxf.;

endsas;
```